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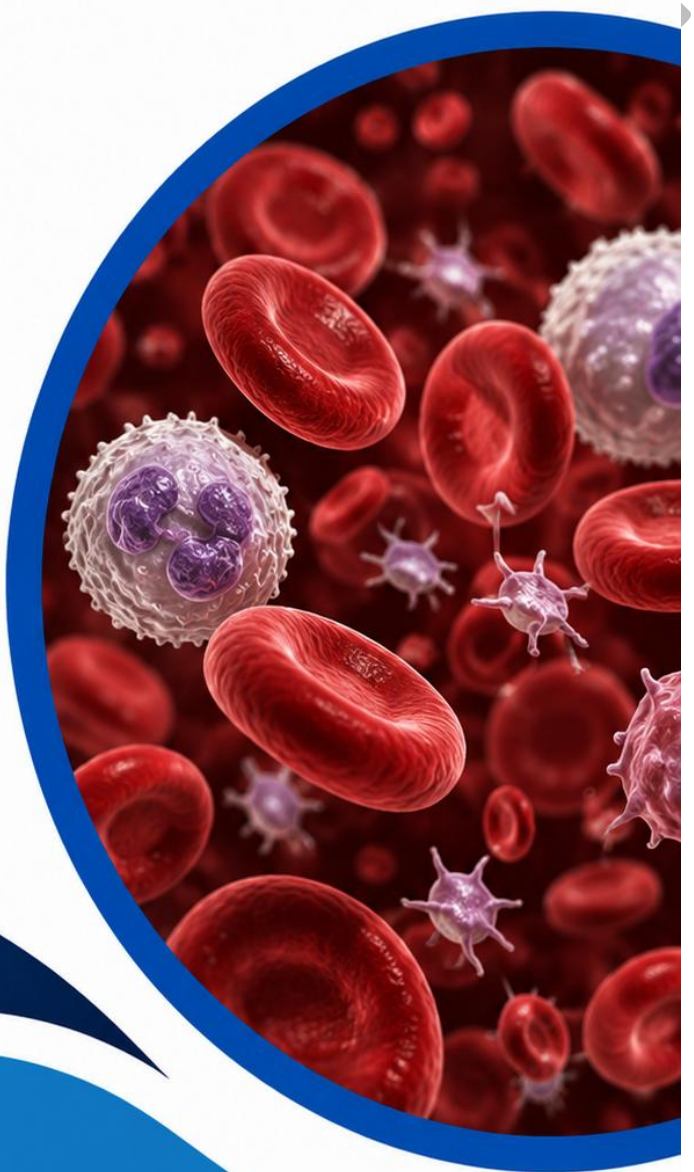
MED 612

HAEMATOLOGY II



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Course code: MED 612

Course title: Haematology II

Course credit load: 2 Units

Series 1: Nutritional and Haemolytic Anaemias

- **Part 1.1: Approach to Anaemia**
    - Sub Part 1.1.1: Classification of anaemia
    - Sub Part 1.1.2: Clinical presentation of anaemia
    - Sub Part 1.1.3: Investigation of anaemia
- **Part 1.2: Nutritional Anaemias I: Iron Deficiency**
    - Sub Part 1.2.1: Pathophysiology and causes of iron deficiency anaemia
    - Sub Part 1.2.2: Clinical presentation and investigation of iron deficiency anaemia
    - Sub Part 1.2.3: Management of iron deficiency anaemia
- **Part 1.3: Nutritional Anaemias II: Megaloblastic Anaemia**
    - Sub Part 1.3.1: Pathophysiology of megaloblastic anaemia
    - Sub Part 1.3.2: Vitamin B12 deficiency
    - Sub Part 1.3.3: Folate deficiency
- **Part 1.4: Haemolytic Anaemia**
    - Sub Part 1.4.1: Classification and mechanisms of haemolysis
    - Sub Part 1.4.2: Clinical presentation and investigation of haemolytic anaemia
    - Sub Part 1.4.3: Causes and management of haemolytic anaemia

Introduction

This opening Series of **Haematology II** builds the structured framework for approaching anaemia before working through two genuinely major categories in depth, the **nutritional anaemias**, arising from a deficiency of a specific building block red cell production depends on, and **haemolytic anaemia**, arising instead from premature red cell destruction rather than inadequate production.

The aim of this Series is to equip you with the ability to classify anaemia and describe its presentation and investigation, describe the pathophysiology, presentation, and management of iron deficiency anaemia, describe megaloblastic anaemia including vitamin B12 and folate deficiency, and classify haemolytic anaemia and describe its mechanisms, presentation, causes, and management.

This Series opens with the **approach to anaemia**, moves through **nutritional anaemias I: iron deficiency** and **nutritional anaemias II: megaloblastic anaemia**, and closes with **haemolytic anaemia**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** classify anaemia and describe its clinical presentation
- **SLO 1.2:** describe the investigation of anaemia
- **SLO 1.3:** describe the pathophysiology, presentation, and management of iron deficiency anaemia
- **SLO 1.4:** describe megaloblastic anaemia
- **SLO 1.5:** describe vitamin B12 deficiency
- **SLO 1.6:** describe folate deficiency
- **SLO 1.7:** classify haemolytic anaemia and describe its mechanisms and clinical presentation
- **SLO 1.8:** describe the causes and management of haemolytic anaemia

1.1 Approach to Anaemia

1.1.1 classification of anaemia

Sorting by red cell size, the genuinely powerful starting point

Anaemia, a reduction in haemoglobin concentration below the normal range for age and sex, is classified according to **mean corpuscular volume**, the average red cell size, into **microcytic**, small red cells, **normocytic**, normal-sized red cells, and **macrocytic**, large red cells, a classification carrying genuinely powerful diagnostic value, since specific categories of anaemia characteristically fall within one of these three size groups.

Microcytic anaemia most commonly reflects iron deficiency, discussed in depth in the following Part of this Series, **macrocytic anaemia** most commonly reflects megaloblastic anaemia from vitamin B12 or folate deficiency, discussed further later in this Series, and **normocytic anaemia** has a genuinely wider differential, including anaemia of chronic disease and many causes of haemolysis, discussed in the closing Part of this Series.

Fill in the blank: Anaemia is classified according to mean corpuscular volume into microcytic, normocytic, and _____.

1.1.2 clinical presentation of anaemia

Symptoms reflecting reduced oxygen delivery to tissues

Anaemia presents with fatigue, breathlessness on exertion, and, in more significant cases, palpitations and dizziness, symptoms directly reflecting reduced oxygen delivery to tissues, and the severity and rate of symptom development depend heavily on both the degree of anaemia and how rapidly it has developed, since gradual, chronic anaemia allows genuine physiological compensation that can mask the severity of even a genuinely low haemoglobin level.

Examination findings include **pallor**, most reliably assessed at the conjunctivae and nail beds given the genuine variability of skin colour assessment across different skin tones, and, in more significant anaemia, tachycardia and, in severe cases, a flow murmur reflecting increased cardiac output compensating for reduced oxygen-carrying capacity, alongside specific signs relevant to the underlying cause covered across the remainder of this Series.

Fill in the blank: Pallor is most reliably assessed at the conjunctivae and nail beds given the genuine variability of _____ colour assessment.

1.1.3 investigation of anaemia

The full blood count and blood film as the essential starting point

The **full blood count**, providing haemoglobin concentration, mean corpuscular volume, and other red cell indices, forms the essential starting point for investigating any anaemia, and the **blood film**, direct microscopic examination of the red cells, provides genuinely valuable additional morphological information, including specific red cell shape abnormalities that can themselves point directly towards a specific underlying diagnosis.

Further investigation, guided by the initial mean corpuscular volume classification already discussed, includes iron studies for suspected microcytic anaemia, vitamin B12 and folate levels for suspected macrocytic anaemia, and reticulocyte count, alongside haemolysis-specific

investigations discussed in the closing Part of this Series, for suspected normocytic anaemia with a haemolytic cause genuinely suspected.

Fill in the blank: The blood film provides valuable additional morphological information, including specific red cell shape _____.

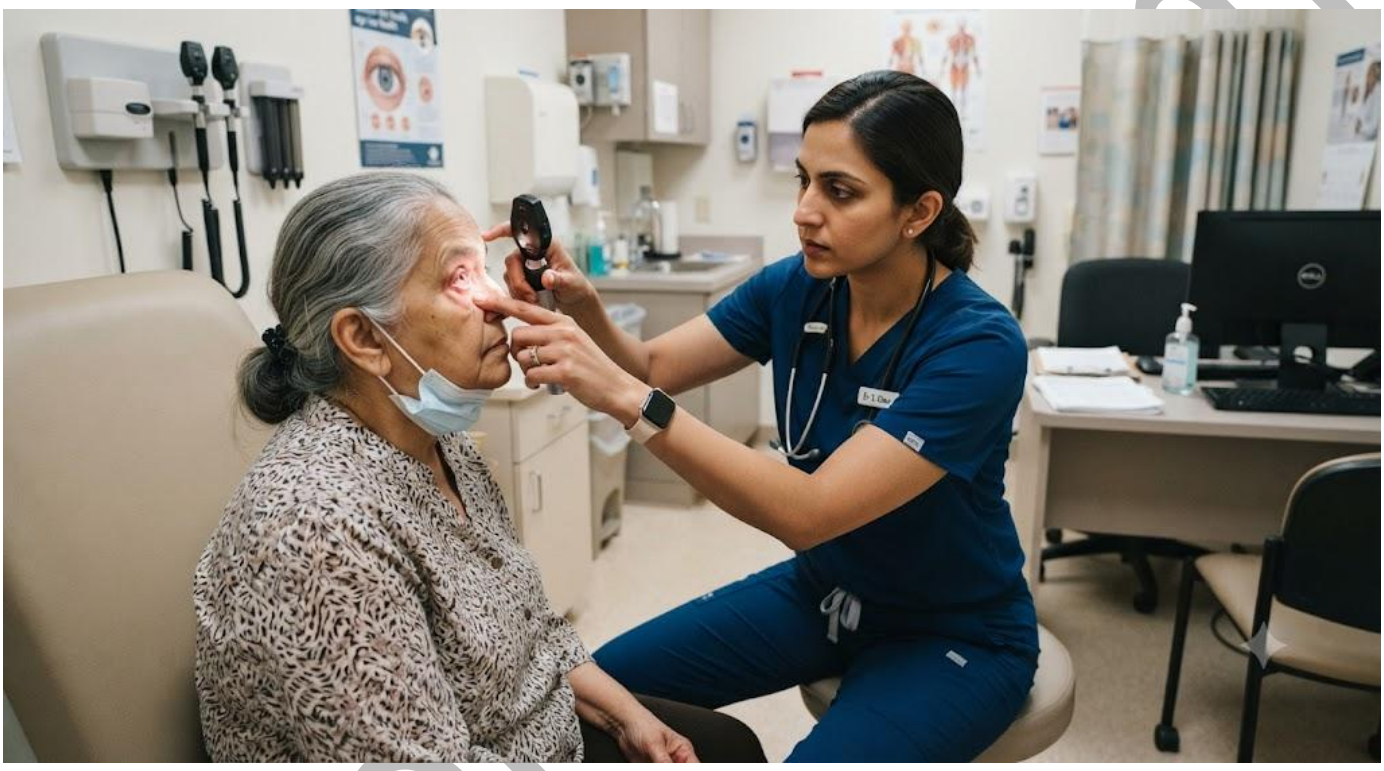

Figure 1.1: A clinician examining conjunctival pallor as a sign of anaemia.

Pilot questions 1.1

1. Describe the classification of anaemia by mean corpuscular volume. (Linked to SLO 1.1)
2. List the causes typically associated with each mean corpuscular volume category. (Linked to SLO 1.1)
3. Describe the symptoms and signs of anaemia. (Linked to SLO 1.1)
4. Explain why chronic, gradual anaemia can mask genuine severity. (Linked to SLO 1.1)
5. Describe the role of the full blood count and blood film in investigating anaemia. (Linked to SLO 1.2)

1.2 Nutritional Anaemias I: Iron Deficiency

1.2.1 pathophysiology and causes of iron deficiency anaemia

The most common cause of anaemia worldwide

Iron deficiency anaemia, the most common cause of anaemia worldwide, results from inadequate iron available for haemoglobin synthesis, whether from inadequate dietary intake, malabsorption, particularly coeliac disease already discussed in an earlier course of this programme, or, genuinely importantly, chronic blood loss, most commonly gastrointestinal or, in women of reproductive age, menstrual, each requiring a genuinely distinct diagnostic and management approach.

In an adult, particularly a man or postmenopausal woman, presenting with genuinely unexplained iron deficiency anaemia, active investigation for an occult gastrointestinal source of blood loss, including the malignancy already discussed in an earlier course of this programme, is genuinely essential rather than assuming a purely nutritional or unidentified cause, given the potentially serious consequences of a missed underlying diagnosis.

Fill in the blank: In unexplained iron deficiency anaemia, active investigation for an occult gastrointestinal source of blood _____ is genuinely essential.

1.2.2 clinical presentation and investigation of iron deficiency anaemia

Anaemia symptoms alongside specific iron-related features

Beyond the general symptoms of anaemia already discussed in Part 1.1, iron deficiency can produce specific additional features including **koilonychia**, spoon-shaped nails, **angular stomatitis**, cracking at the corners of the mouth, and, rarely, **pica**, craving for non-food substances such as ice or dirt, findings that, while genuinely specific to iron deficiency when present, are absent in a considerable proportion of affected patients.

Iron studies, including serum ferritin, the most reliable single indicator of total body iron stores, alongside serum iron and total iron-binding capacity, confirm the diagnosis, though ferritin, as an acute phase reactant, can be genuinely falsely elevated in the presence of inflammation or infection, meaning interpretation genuinely requires clinical context rather than the ferritin value alone in isolation.

Fill in the blank: Serum ferritin can be genuinely falsely elevated in the presence of inflammation or _____.

1.2.3 management of iron deficiency anaemia

Replacing the deficient iron, and treating the underlying cause

Oral iron replacement, the standard first-line treatment, is genuinely effective though frequently limited by gastrointestinal side effects including constipation and nausea, and, where oral iron is genuinely poorly tolerated or malabsorption prevents adequate absorption, **intravenous iron** offers an effective alternative, delivering iron directly without relying on intestinal absorption.

Genuinely importantly, treating the underlying cause of iron deficiency, whether dietary modification, treating identified malabsorption, or addressing an identified source of chronic blood loss, remains essential alongside iron replacement itself, since replacing iron alone without addressing an ongoing source of loss will genuinely fail to achieve lasting correction of the anaemia.

Fill in the blank: Intravenous iron delivers iron directly without relying on intestinal _____.

Table 1.1: Interpreting iron studies

Test	Typical finding in iron deficiency	Genuine interpretive caution
Serum ferritin	Low	Falsely elevated by inflammation
Serum iron	Low	Genuinely variable throughout the day
Total iron-binding capacity	Elevated	Reflects transferrin, not iron stores directly

Pilot questions 1.2

1. List the causes of iron deficiency anaemia. (Linked to SLO 1.3)
2. Explain why unexplained iron deficiency anaemia requires active investigation for an occult source. (Linked to SLO 1.3)
3. Describe koilonychia and angular stomatitis. (Linked to SLO 1.3)
4. Explain why ferritin interpretation requires clinical context. (Linked to SLO 1.3)
5. Describe the management options for iron deficiency anaemia. (Linked to SLO 1.3)

1.3 Nutritional Anaemias II: Megaloblastic Anaemia

1.3.1 pathophysiology of megaloblastic anaemia

Impaired DNA synthesis producing genuinely abnormal, large red cells

Megaloblastic anaemia, resulting from impaired DNA synthesis within developing red blood cell precursors, most commonly from vitamin B12 or folate deficiency, produces genuinely large, abnormally shaped red cells, since impaired DNA synthesis specifically slows nuclear maturation relative to cytoplasmic maturation, a genuinely distinctive cellular mechanism directly underlying the characteristic macrocytic morphology seen on blood film examination.

Since both vitamin B12 and folate are genuinely essential cofactors for the same DNA synthesis pathway, deficiency of either produces a genuinely similar megaloblastic blood picture, meaning distinguishing between the two specific deficiencies, discussed in the following two sub-Parts of this Part, requires specific laboratory testing rather than relying on the blood film appearance alone to determine which specific deficiency is responsible.

Fill in the blank: Impaired DNA synthesis specifically slows nuclear maturation relative to _____ maturation in megaloblastic anaemia.

1.3.2 vitamin b12 deficiency

A deficiency with genuine neurological, not just haematological, consequences

Vitamin B12 deficiency most commonly results from **pernicious anaemia**, an autoimmune condition destroying gastric parietal cells and reducing intrinsic factor production, essential for vitamin B12 absorption in the terminal ileum already discussed in an earlier course of this programme, or, less commonly, from dietary insufficiency, particularly in strict vegans, or malabsorption from terminal ileal disease.

Beyond the haematological consequences already discussed, vitamin B12 deficiency can produce genuine neurological complications, including peripheral neuropathy and, in severe, longstanding deficiency, subacute combined degeneration of the spinal cord, already discussed in an earlier course of this programme, a genuinely important complication since neurological damage may not fully reverse even with appropriate treatment if the deficiency has been allowed to persist untreated for a genuinely prolonged period.

Fill in the blank: Pernicious anaemia is an autoimmune condition destroying gastric parietal cells and reducing intrinsic _____ production.

1.3.3 folate deficiency

A genuinely more rapidly depleted, dietary-dependent deficiency

Folate deficiency, most commonly resulting from inadequate dietary intake given the body's comparatively limited folate stores, is also seen with malabsorption, including coeliac disease already discussed, increased folate requirement, particularly pregnancy given the genuinely significant folate demand fetal development creates, and, less commonly, certain medications interfering with folate metabolism.

Genuinely important, and worth actively remembering, folate deficiency should never be treated in isolation without first excluding or correcting a coexisting vitamin B12 deficiency, since folate replacement alone can correct the haematological picture while genuinely allowing any underlying vitamin B12-related neurological damage to progress unchecked, a genuinely serious, well-recognised clinical pitfall this Part aims to firmly establish awareness of.

Fill in the blank: Folate replacement alone can correct the haematological picture while allowing underlying vitamin B12-related neurological damage to progress _____.

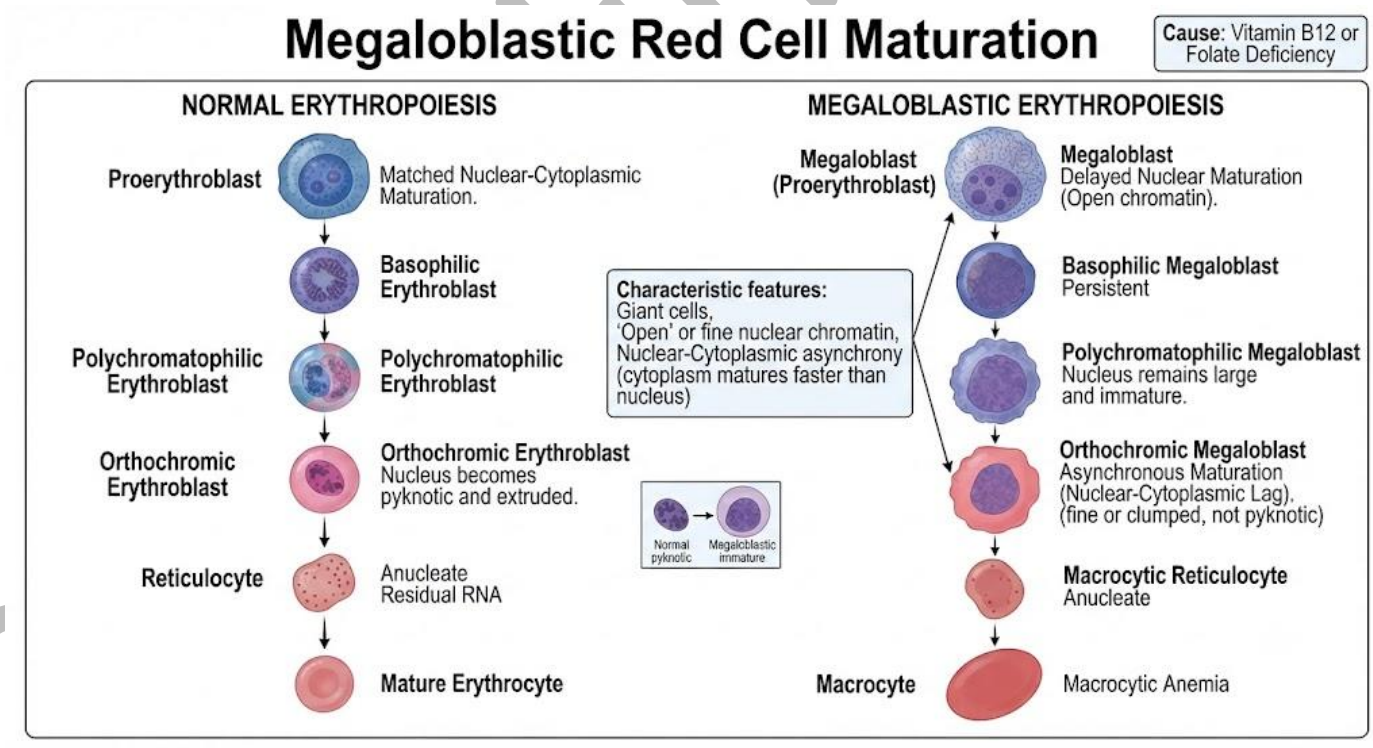

Figure 1.2: A labelled diagram comparing normal red cell maturation with megaloblastic maturation.

Pilot questions 1.3

1. Describe the pathophysiology of megaloblastic anaemia. (Linked to SLO 1.4)
2. Explain why distinguishing vitamin B12 from folate deficiency requires specific testing. (Linked to SLO 1.4)
3. Describe pernicious anaemia. (Linked to SLO 1.5)
4. List the neurological complications of vitamin B12 deficiency. (Linked to SLO 1.5)
5. Explain why folate should never be given in isolation without excluding vitamin B12 deficiency. (Linked to SLO 1.6)

1.4 Haemolytic Anaemia

1.4.1 classification and mechanisms of haemolysis

Premature red cell destruction, from within the cell or beyond it

Haemolytic anaemia, resulting from premature red cell destruction exceeding the bone marrow's capacity to compensate through increased production, is classified as **intrinsic**, resulting from an inherent red cell abnormality such as membrane, enzyme, or haemoglobin defects, or **extrinsic**, resulting from an external factor destroying otherwise normal red cells, such as an autoimmune process or mechanical destruction.

Haemolysis is further classified by location as **intravascular**, red cell destruction occurring directly within the circulation, or **extravascular**, red cell destruction occurring within the reticuloendothelial system, particularly the spleen, a distinction carrying genuine relevance to the specific pattern of laboratory findings and clinical features each mechanism characteristically produces.

Fill in the blank: Haemolysis is classified as intrinsic, from an inherent red cell abnormality, or extrinsic, from an external _____.

1.4.2 clinical presentation and investigation of haemolytic anaemia

Anaemia symptoms alongside genuine evidence of red cell breakdown

Beyond the general anaemia symptoms already discussed, haemolytic anaemia can produce **jaundice**, from increased bilirubin production as red cells are broken down, and, in more significant, longstanding haemolysis, gallstones from chronic excess bilirubin excretion, and

splenomegaly reflecting increased reticuloendothelial activity, particularly in extravascular haemolysis already discussed in the previous sub-Part.

Investigation confirms haemolysis through elevated reticulocyte count, reflecting compensatory increased red cell production, elevated unconjugated bilirubin and lactate dehydrogenase, reflecting red cell breakdown, and reduced haptoglobin, a protein binding and clearing free haemoglobin released during haemolysis, together forming a genuinely characteristic laboratory pattern confirming the haemolytic process before its specific underlying cause is pursued further.

Fill in the blank: Reduced haptoglobin reflects a protein binding and clearing free _____ released during haemolysis.

1.4.3 causes and management of haemolytic anaemia

A genuinely wide differential, with cause-directed treatment

Causes of haemolytic anaemia include **autoimmune haemolytic anaemia**, antibody-mediated red cell destruction, hereditary conditions including hereditary spherocytosis, a red cell membrane defect, and glucose-6-phosphate dehydrogenase deficiency, an enzyme defect, and mechanical causes including prosthetic heart valves already discussed in an earlier course of this programme, each requiring a genuinely distinct specific investigation and management approach.

Management is genuinely cause-specific, with corticosteroids and, where necessary, other immunosuppressive treatment for autoimmune haemolytic anaemia, avoidance of specific oxidative triggers for glucose-6-phosphate dehydrogenase deficiency, and, for selected patients with significant, ongoing extravascular haemolysis genuinely refractory to medical management, **splenectomy**, surgical removal of the spleen, offering a further treatment option given the spleen's genuine central role in extravascular red cell destruction.

Fill in the blank: Splenectomy offers a treatment option given the spleen's genuine central role in _____ red cell destruction.

Table 1.2: Comparing causes of haemolytic anaemia

Cause	Mechanism	Key management approach
Autoimmune haemolytic anaemia	Antibody-mediated destruction	Corticosteroids, immunosuppression
Hereditary spherocytosis	Red cell membrane defect	Splenectomy in selected cases
G6PD deficiency	Enzyme defect, oxidative sensitivity	Avoidance of oxidative triggers

Pilot questions 1.4

1. Distinguish intrinsic from extrinsic haemolysis. (Linked to SLO 1.7)
2. Distinguish intravascular from extravascular haemolysis. (Linked to SLO 1.7)
3. Describe the clinical features suggesting haemolytic anaemia. (Linked to SLO 1.7)
4. List the laboratory findings confirming haemolysis. (Linked to SLO 1.8)
5. List causes of haemolytic anaemia and their management. (Linked to SLO 1.8)

Series Summary

This opening Series built the framework for approaching anaemia before covering nutritional and haemolytic anaemias in depth. Part 1.1 covered the classification, presentation, and investigation of anaemia, while Part 1.2 turned to iron deficiency anaemia. Part 1.3 covered megaloblastic anaemia, vitamin B12 deficiency, and folate deficiency, and Part 1.4 closed with haemolytic anaemia.

You should now be able to classify, investigate, and describe the specific nutritional and haemolytic anaemias covered across all four Parts of this Series, meeting the outcomes set for this Series. Series 2 turns next to aplastic anaemia and haemoglobinopathies.

Glossary of Terms

- **Angular stomatitis:** cracking at the corners of the mouth, a feature of iron deficiency.
- **Autoimmune haemolytic anaemia:** antibody-mediated red cell destruction.
- **G6PD deficiency:** an enzyme defect causing haemolysis with oxidative triggers.
- **Haptoglobin:** a protein binding and clearing free haemoglobin released during haemolysis.
- **Hereditary spherocytosis:** a red cell membrane defect causing haemolytic anaemia.
- **Iron deficiency anaemia:** the most common cause of anaemia worldwide, from inadequate iron for haemoglobin synthesis.
- **Koilonychia:** spoon-shaped nails, a feature of iron deficiency.
- **Megaloblastic anaemia:** macrocytic anaemia from impaired DNA synthesis, commonly vitamin B12 or folate deficiency.

- **Pernicious anaemia:** autoimmune destruction of gastric parietal cells reducing intrinsic factor production.
- **Reticulocyte count:** a measure of new red cell production, elevated in compensated haemolysis.
- **Serum ferritin:** the most reliable single indicator of total body iron stores.
- **Splenectomy:** surgical removal of the spleen, used in selected extravascular haemolysis.

Concept Check Questions [Series 1]

Objective questions

1. Anaemia is classified according to mean corpuscular volume into microcytic, normocytic, and _____. (Linked to SLO 1.1)
2. In unexplained iron deficiency anaemia, active investigation for an occult gastrointestinal source of blood _____ is genuinely essential. (Linked to SLO 1.3)
3. Impaired DNA synthesis specifically slows nuclear maturation relative to _____ maturation in megaloblastic anaemia. (Linked to SLO 1.4)
4. Pernicious anaemia is an autoimmune condition destroying gastric parietal cells and reducing intrinsic _____ production. (Linked to SLO 1.5)
5. Haemolysis is classified as intrinsic, from an inherent red cell abnormality, or extrinsic, from an external _____. (Linked to SLO 1.7)

Short-answer questions

6. List the causes typically associated with each mean corpuscular volume category. (Linked to SLO 1.1)
7. Describe koilonychia and angular stomatitis. (Linked to SLO 1.3)
8. List the neurological complications of vitamin B12 deficiency. (Linked to SLO 1.5)
9. Explain why folate should never be given in isolation without excluding vitamin B12 deficiency. (Linked to SLO 1.6)
10. List the laboratory findings confirming haemolysis. (Linked to SLO 1.8)

Long-answer questions

11. Discuss the classification, presentation, and investigation of anaemia. (Linked to SLO 1.1, 1.2)
12. Describe the pathophysiology, presentation, and management of iron deficiency anaemia. (Linked to SLO 1.3)
13. Discuss megaloblastic anaemia, including vitamin B12 and folate deficiency. (Linked to SLO 1.4, 1.5, 1.6)

14. Describe the classification, mechanisms, and presentation of haemolytic anaemia. (Linked to SLO 1.7)
15. Discuss the causes and management of haemolytic anaemia. (Linked to SLO 1.8)

Answers to Concept Check Questions [Series 1]

Objective questions

1. Macrocytic.
2. Loss.
3. Cytoplasmic.
4. Factor.
5. Factor.

Short-answer questions

6. Microcytic suggests iron deficiency, macrocytic suggests megaloblastic anaemia, and normocytic has a wide differential.
7. Koilonychia is spoon-shaped nails, while angular stomatitis is cracking at the corners of the mouth.
8. Complications include peripheral neuropathy and subacute combined degeneration of the spinal cord.
9. Folate alone can correct the blood picture while allowing underlying B12-related neurological damage to progress unchecked.
10. Findings include elevated reticulocyte count, unconjugated bilirubin, lactate dehydrogenase, and reduced haptoglobin.

Long-answer questions

11. **Basic response:** Anaemia is classified by mean corpuscular volume into microcytic, normocytic, and macrocytic; presentation includes fatigue and breathlessness; investigation begins with full blood count and blood film, followed by targeted testing.

    Value-added response: A value-added response notes that chronic, gradual anaemia allows physiological compensation that can mask genuine severity.

12. **Basic response:** Iron deficiency results from inadequate intake, malabsorption, or chronic blood loss; presentation includes koilonychia and angular stomatitis alongside general anaemia symptoms; management uses oral or intravenous iron alongside treating the underlying cause.

Value-added response: A value-added response notes that unexplained iron deficiency anaemia in an adult requires active investigation for an occult gastrointestinal source.

13. **Basic response:** Megaloblastic anaemia results from impaired DNA synthesis, commonly from vitamin B12 or folate deficiency; B12 deficiency, often from pernicious anaemia, carries neurological risk; folate deficiency is more rapidly depleted and dietary-dependent.

    Value-added response: A value-added response notes that folate should never be replaced in isolation without excluding coexisting B12 deficiency.

14. **Basic response:** Haemolytic anaemia is classified as intrinsic or extrinsic, and intravascular or extravascular; presentation includes jaundice, gallstones, and splenomegaly alongside general anaemia symptoms.

    Value-added response: A value-added response notes that laboratory confirmation includes elevated reticulocytes, bilirubin, and lactate dehydrogenase with reduced haptoglobin.

15. **Basic response:** Causes include autoimmune haemolytic anaemia, hereditary spherocytosis, and G6PD deficiency, each managed with a cause-specific approach.

    Value-added response: A value-added response notes that splenectomy offers a further treatment option for refractory extravascular haemolysis.

Answers to Pilot Questions [Series 1]

Part 1.1

1. Anaemia is classified as microcytic, normocytic, or macrocytic based on mean corpuscular volume.
2. Microcytic suggests iron deficiency, macrocytic suggests megaloblastic anaemia, and normocytic has a wide differential.
3. Symptoms include fatigue, breathlessness, palpitations, and dizziness; signs include pallor and tachycardia.
4. Gradual anaemia allows physiological compensation, masking severity that might otherwise be obvious.

5. The full blood count provides indices, while the blood film provides morphological information supporting diagnosis.

Part 1.2

1. Causes include inadequate intake, malabsorption, and chronic blood loss, gastrointestinal or menstrual.
2. Active investigation excludes a serious underlying cause such as gastrointestinal malignancy.
3. Koilonychia is spoon-shaped nails; angular stomatitis is cracking at the corners of the mouth.
4. Ferritin is an acute phase reactant and can be falsely elevated by inflammation or infection.
5. Options include oral iron replacement or intravenous iron where oral is poorly tolerated or malabsorbed.

Part 1.3

1. Megaloblastic anaemia results from impaired DNA synthesis slowing nuclear relative to cytoplasmic maturation.
2. Both deficiencies produce a similar blood picture, requiring specific testing to distinguish which is responsible.
3. Pernicious anaemia is autoimmune destruction of gastric parietal cells, reducing intrinsic factor production.
4. Complications include peripheral neuropathy and subacute combined degeneration of the spinal cord.
5. Folate alone can correct the blood picture while allowing underlying B12-related neurological damage to progress.

Part 1.4

1. Intrinsic haemolysis results from an inherent red cell defect, while extrinsic results from an external factor.
2. Intravascular haemolysis occurs within the circulation, while extravascular occurs in the reticuloendothelial system.
3. Features include jaundice, gallstones, and splenomegaly alongside general anaemia symptoms.
4. Findings include elevated reticulocyte count, bilirubin, and lactate dehydrogenase, with reduced haptoglobin.
5. Causes include autoimmune haemolytic anaemia, hereditary spherocytosis, and G6PD deficiency, each with specific management.

References and Attributions [Series 1]

- Hoffbrand, A. V., & Steensma, D. P. (2019). Hoffbrand's Essential Haematology (8th ed.). Wiley-Blackwell.
- Kumar, P., & Clark, M. (2020). Kumar and Clark's Clinical Medicine (10th ed.). Elsevier.
- British Society for Haematology (2021). Guideline for the Management of Iron Deficiency Anaemia. British Journal of Haematology.
- British Society for Haematology (2014). Guidelines for the Diagnosis and Management of Cobalamin and Folate Disorders. British Journal of Haematology.

Figures, Plates, Tables, and Boxes

- Figure 1.1: A clinician examining conjunctival pallor as a sign of anaemia. AI-generated using the prompt: "Create a realistic clinical illustration titled Examining Conjunctival Pallor, showing a clinician gently pulling down a seated patient's lower eyelid to examine the conjunctiva, clinical examination room setting. Clean clinical illustration style, no text."
- Table 1.1: Interpreting iron studies. AI-generated using the prompt: "Create a clean reference table titled Interpreting Iron Studies, listing test, typical finding in iron deficiency, and genuine interpretive caution. Simple clinical reference table style with outside border."
- Figure 1.2: A labelled diagram comparing normal red cell maturation with megaloblastic maturation. AI-generated using the prompt: "Create a clean, accurate labelled educational diagram titled Megaloblastic Red Cell Maturation, showing two side-by-side sequences of red blood cell precursor maturation, one labelled normal with matched nuclear and cytoplasmic development, and one labelled megaloblastic with delayed nuclear maturation relative to cytoplasm. Educational anatomical diagram style, no photographic content."
- Table 1.2: Comparing causes of haemolytic anaemia. AI-generated using the prompt: "Create a clean reference table titled Comparing Causes of Haemolytic Anaemia, listing cause, mechanism, and key management approach. Simple clinical reference table style with outside border."

Course code: MED 612

Course title: Haematology II

Course credit load: 2 Units

Series 2: Aplastic Anaemia and Haemoglobinopathies

- **Part 2.1: Aplastic Anaemia I: Pathophysiology and Causes**
  - Sub Part 2.1.1: Pathophysiology of aplastic anaemia
  - Sub Part 2.1.2: Causes of aplastic anaemia
  - Sub Part 2.1.3: Clinical presentation of aplastic anaemia
- **Part 2.2: Aplastic Anaemia II: Diagnosis and Management**
  - Sub Part 2.2.1: Investigation and diagnosis of aplastic anaemia
  - Sub Part 2.2.2: Management of aplastic anaemia
  - Sub Part 2.2.3: Prognosis and complications of aplastic anaemia
- **Part 2.3: Sickle Cell Disease**
  - Sub Part 2.3.1: Pathophysiology and genetics of sickle cell disease
  - Sub Part 2.3.2: Clinical presentation and complications of sickle cell disease
  - Sub Part 2.3.3: Management of sickle cell disease
- **Part 2.4: Thalassaemia**
  - Sub Part 2.4.1: Pathophysiology and genetics of thalassaemia
  - Sub Part 2.4.2: Clinical presentation of thalassaemia
  - Sub Part 2.4.3: Management of thalassaemia

Introduction

This Series turns to two genuinely distinct categories of haematological disease, **aplastic anaemia**, a genuinely serious failure of the bone marrow itself to produce blood cells of any lineage, and the **haemoglobinopathies**, inherited disorders of haemoglobin structure or

production, sickle cell disease and thalassaemia, each producing a genuinely distinct, characteristic clinical pattern rooted in a specific, well-understood molecular abnormality.

The aim of this Series is to equip you with an understanding of the pathophysiology, causes, presentation, investigation, management, prognosis, and complications of aplastic anaemia, and the pathophysiology, genetics, presentation, and management of sickle cell disease and thalassaemia.

This Series opens with **aplastic anaemia I: pathophysiology and causes**, moves through **aplastic anaemia II: diagnosis and management** and **sickle cell disease**, and closes with **thalassaemia**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 2.1:** describe the pathophysiology and causes of aplastic anaemia
- **SLO 2.2:** describe the clinical presentation of aplastic anaemia
- **SLO 2.3:** discuss the investigation and management of aplastic anaemia
- **SLO 2.4:** describe the prognosis and complications of aplastic anaemia
- **SLO 2.5:** describe the pathophysiology, genetics, and clinical presentation of sickle cell disease
- **SLO 2.6:** discuss the management of sickle cell disease
- **SLO 2.7:** describe the pathophysiology, genetics, and clinical presentation of thalassaemia
- **SLO 2.8:** discuss the management of thalassaemia

2.1 Aplastic Anaemia I: Pathophysiology and Causes

2.1.1 pathophysiology of aplastic anaemia

Failure of the bone marrow itself, affecting all three cell lineages

Aplastic anaemia, a genuinely serious condition resulting from failure of the bone marrow's haematopoietic stem cells, produces **pancytopenia**, a reduction in all three major blood cell lineages, red cells, white cells, and platelets, a genuinely distinctive pattern distinguishing it from the anaemias already discussed in Series 1, which typically affect red cells in isolation without significantly reducing white cell or platelet numbers.

The underlying mechanism most commonly involves genuine autoimmune destruction of haematopoietic stem cells, and this genuinely global marrow failure, affecting the production of every blood cell lineage simultaneously, directly explains the genuinely wide-ranging combination of symptoms this condition produces, discussed further in the closing sub-Part of this Part, reflecting the combined consequences of deficiency across all three affected cell lines.

Fill in the blank: Aplastic anaemia produces pancytopenia, a reduction in all three major blood cell _____.

2.1.2 causes of aplastic anaemia

Acquired and inherited causes, with a genuinely important idiopathic category

Causes of aplastic anaemia include acquired causes, certain medications, viral infection, and radiation exposure, alongside inherited causes, such as Fanconi anaemia, a genetic condition affecting DNA repair, though genuinely importantly, a considerable proportion of cases remain **idiopathic**, with no specific identifiable cause found despite thorough investigation, reflecting the genuinely incomplete understanding of this condition's underlying trigger in many affected patients.

Identifying a specific causative agent, where genuinely possible, carries direct management relevance, since discontinuing an implicated medication represents an essential, immediate first step, while idiopathic cases, and those with a confirmed autoimmune mechanism already discussed in the previous sub-Part, proceed directly to the specific treatment approaches discussed in the following Part of this Series.

Fill in the blank: A considerable proportion of aplastic anaemia cases remain _____, with no specific identifiable cause found.

2.1.3 clinical presentation of aplastic anaemia

A genuinely combined pattern reflecting deficiency across all three lineages

Aplastic anaemia presents with the general symptoms of anaemia already discussed in Series 1, reflecting red cell deficiency, alongside recurrent or unusually severe infections reflecting **neutropenia**, deficient neutrophil white cells, and easy bruising, petechiae, and mucosal bleeding reflecting **thrombocytopenia**, deficient platelets, a genuinely characteristic triad of combined symptoms directly reflecting the pancytopenia already established as this condition's defining haematological feature.

This genuinely combined symptom pattern, rather than isolated anaemia symptoms alone, should immediately raise suspicion for aplastic anaemia or another cause of pancytopenia, discussed further among the myeloproliferative and leukaemic conditions covered in a later Series of this course, and prompt recognition of this specific combined pattern is genuinely essential given the significant potential severity of untreated aplastic anaemia.

Fill in the blank: Petechiae and mucosal bleeding in aplastic anaemia reflect thrombocytopenia, deficient _____.

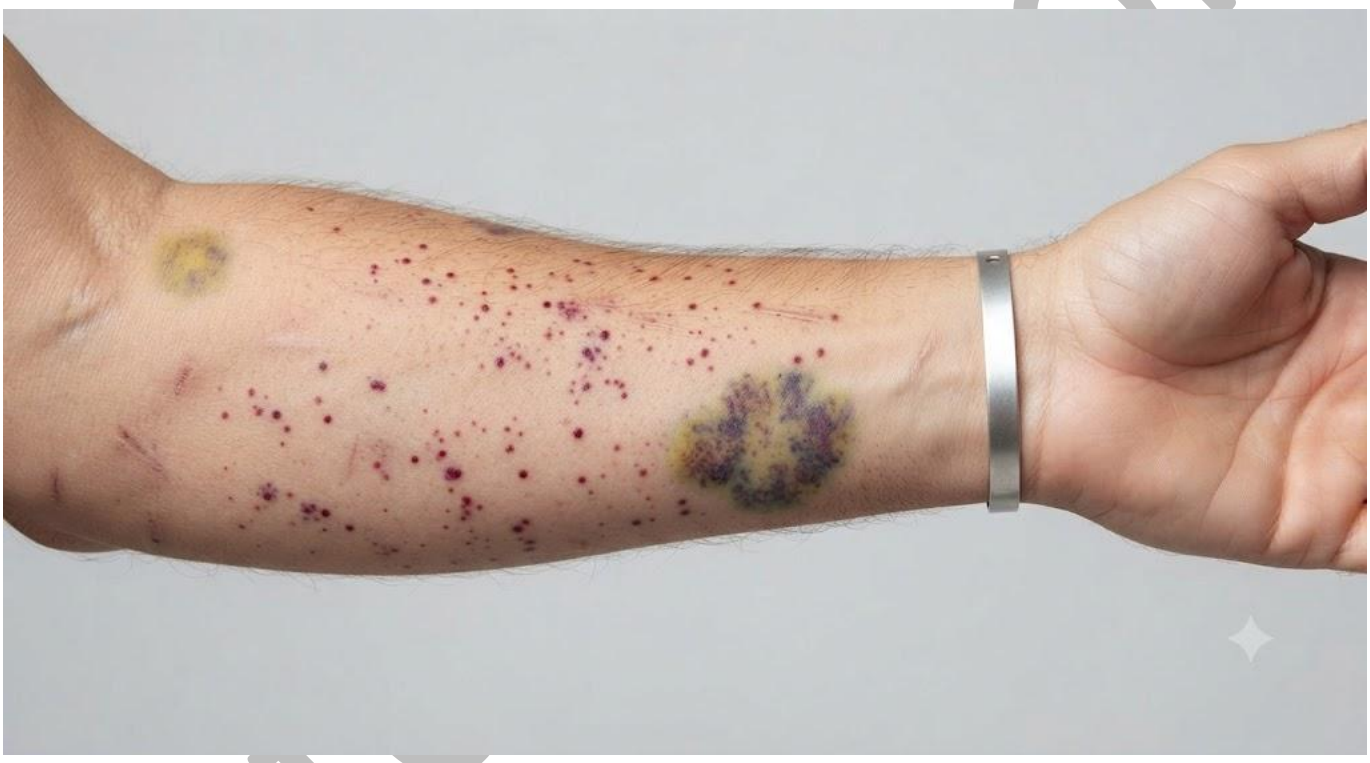

Figure 2.1: Petechiae and bruising on the forearm reflecting thrombocytopenia.

Pilot questions 2.1

- Describe pancytopenia. (Linked to SLO 2.1)
- Describe the underlying mechanism of aplastic anaemia. (Linked to SLO 2.1)
- List acquired and inherited causes of aplastic anaemia. (Linked to SLO 2.1)
- Explain the genuine management relevance of identifying a specific causative agent. (Linked to SLO 2.1)
- Describe the combined symptom pattern of aplastic anaemia. (Linked to SLO 2.2)

2.2 Aplastic Anaemia II: Diagnosis and Management

2.2.1 investigation and diagnosis of aplastic anaemia

Confirming pancytopenia, then examining the marrow directly

Full blood count, demonstrating pancytopenia already discussed in the previous Part, alongside **reticulocyte count**, genuinely low given the inadequate marrow response, together provide the initial supporting evidence for aplastic anaemia, and **bone marrow biopsy**, directly examining the marrow's cellular content, is genuinely essential to confirm the diagnosis, demonstrating a **hypocellular marrow**, markedly reduced haematopoietic cells relative to fat content, and excluding other causes of pancytopenia.

Excluding alternative diagnoses, particularly the myeloproliferative and leukaemic conditions already flagged in the previous Part, which can occasionally present with a genuinely similar pancytopenia picture despite a fundamentally different underlying marrow pathology, is a genuinely essential part of the diagnostic process, given how directly different the management approach for these alternative conditions, covered in a later Series of this course, differs from aplastic anaemia management itself.

Fill in the blank: Bone marrow biopsy demonstrates a hypocellular marrow, markedly reduced haematopoietic cells relative to fat _____.

2.2.2 management of aplastic anaemia

Restoring haematopoiesis through transplantation or immunosuppression

Haematopoietic stem cell transplantation, replacing the failed marrow with healthy donor stem cells, offers a genuinely curative treatment option for appropriately selected, typically younger patients with a suitable donor available, and represents the preferred first-line treatment where genuinely feasible given its superior long-term outcome compared with the alternative approaches discussed next.

Immunosuppressive therapy, typically combining antithymocyte globulin and ciclosporin, offers an alternative treatment approach for patients without a suitable transplant donor or those genuinely unsuitable for transplantation, working by suppressing the autoimmune process already discussed as the underlying mechanism in many cases, though generally offering a genuinely less durable, complete response compared with successful transplantation.

Fill in the blank: Immunosuppressive therapy for aplastic anaemia typically combines antithymocyte globulin and _____.

2.2.3 prognosis and complications of aplastic anaemia

A genuinely serious condition with meaningfully improved modern outcomes

Untreated severe aplastic anaemia carries a genuinely poor prognosis, reflecting the significant infection and bleeding risk pancytopenia produces, though modern treatment, particularly successful transplantation in appropriately selected patients, has meaningfully improved overall outcomes, and prompt diagnosis and treatment initiation genuinely, directly influences the likelihood of a favourable long-term result.

Supportive care, including blood and platelet transfusion support and prompt, aggressive treatment of infection given the genuine vulnerability neutropenia produces, remains genuinely essential throughout the treatment course, whether transplantation or immunosuppressive therapy is chosen, and this comprehensive supportive approach, closing this Part's coverage, reflects the same theme of comprehensive, structured care already emphasised throughout this whole course.

Fill in the blank: Supportive care includes blood and platelet transfusion support and prompt, aggressive treatment of _____.

Table 2.1: Comparing transplantation and immunosuppressive therapy for aplastic anaemia

Feature	Stem cell transplantation	Immunosuppressive therapy
Curative potential	Genuinely curative	Generally not curative
Typical candidate	Younger patient with suitable donor	No suitable donor or unsuitable for transplant
Response durability	Durable if successful	Generally less durable

Pilot questions 2.2

1. Describe the investigations used to diagnose aplastic anaemia. (Linked to SLO 2.3)
2. Explain why excluding alternative diagnoses genuinely matters. (Linked to SLO 2.3)
3. Describe stem cell transplantation as a treatment for aplastic anaemia. (Linked to SLO 2.3)
4. Describe immunosuppressive therapy for aplastic anaemia. (Linked to SLO 2.3)
5. Describe supportive care for aplastic anaemia. (Linked to SLO 2.4)

2.3 Sickle Cell Disease

2.3.1 pathophysiology and genetics of sickle cell disease

A single amino acid substitution with genuinely wide-ranging consequences

Sickle cell disease, an autosomal recessive haemoglobinopathy resulting from a single amino acid substitution in the beta-globin chain producing **haemoglobin S**, causes red cells to adopt a characteristic rigid, sickle shape under conditions of reduced oxygen tension, and these genuinely rigid, abnormally shaped cells cause both premature haemolysis, already discussed in the context of general haemolytic anaemia in Series 1, and, genuinely importantly, vascular occlusion.

Sickle cell trait, the heterozygous carrier state with one copy of the abnormal gene, is generally asymptomatic under normal physiological conditions, while **sickle cell disease** itself, the homozygous state with two copies, or compound heterozygous states with certain other haemoglobin variants, produces the genuinely full clinical syndrome discussed in the following sub-Part of this Part.

Fill in the blank: Sickle cell disease results from a single amino acid substitution in the beta-globin chain producing haemoglobin _____.

2.3.2 clinical presentation and complications of sickle cell disease

Vaso-occlusion and its genuinely wide-ranging consequences

Vaso-occlusive crisis, acute, severe pain resulting from sickled cells obstructing small blood vessels, is the most common acute presentation of sickle cell disease, and, given the genuinely widespread vascular distribution this obstruction can affect, presents with pain in genuinely almost any body region, though most classically the limbs, back, and chest, and can be triggered by dehydration, infection, cold exposure, or hypoxia.

Acute chest syndrome, a genuinely serious pulmonary complication presenting with chest pain, breathlessness, and new pulmonary infiltrate on imaging, and **stroke**, resulting from vaso-occlusion affecting the cerebral circulation, represent two of the genuinely most serious acute complications, alongside chronic complications including renal impairment and, given the functional hyposplenism sickle cell disease produces, genuine, meaningfully increased susceptibility to specific bacterial infections.

Fill in the blank: Sickle cell disease produces functional hyposplenism, causing genuine, meaningfully increased susceptibility to specific bacterial _____.

2.3.3 management of sickle cell disease

Preventing crises, managing them promptly when they occur

Acute vaso-occlusive crisis management centres on adequate analgesia, often requiring genuinely significant opioid doses given the severity of pain this condition can produce, alongside hydration, oxygen where genuinely hypoxic, and prompt treatment of any identified precipitating infection, and this prompt, aggressive acute management genuinely reduces the duration and severity of an individual crisis episode.

Hydroxyurea, increasing production of fetal haemoglobin, which genuinely interferes with sickling, reduces the frequency of vaso-occlusive crises in appropriately selected patients, and preventive measures including pneumococcal vaccination given the hyposplenism-related infection risk already discussed, and prophylactic penicillin in children specifically, together form a genuinely comprehensive preventive approach complementing the acute crisis management already established.

Fill in the blank: Hydroxyurea increases production of fetal haemoglobin, which genuinely interferes with _____.

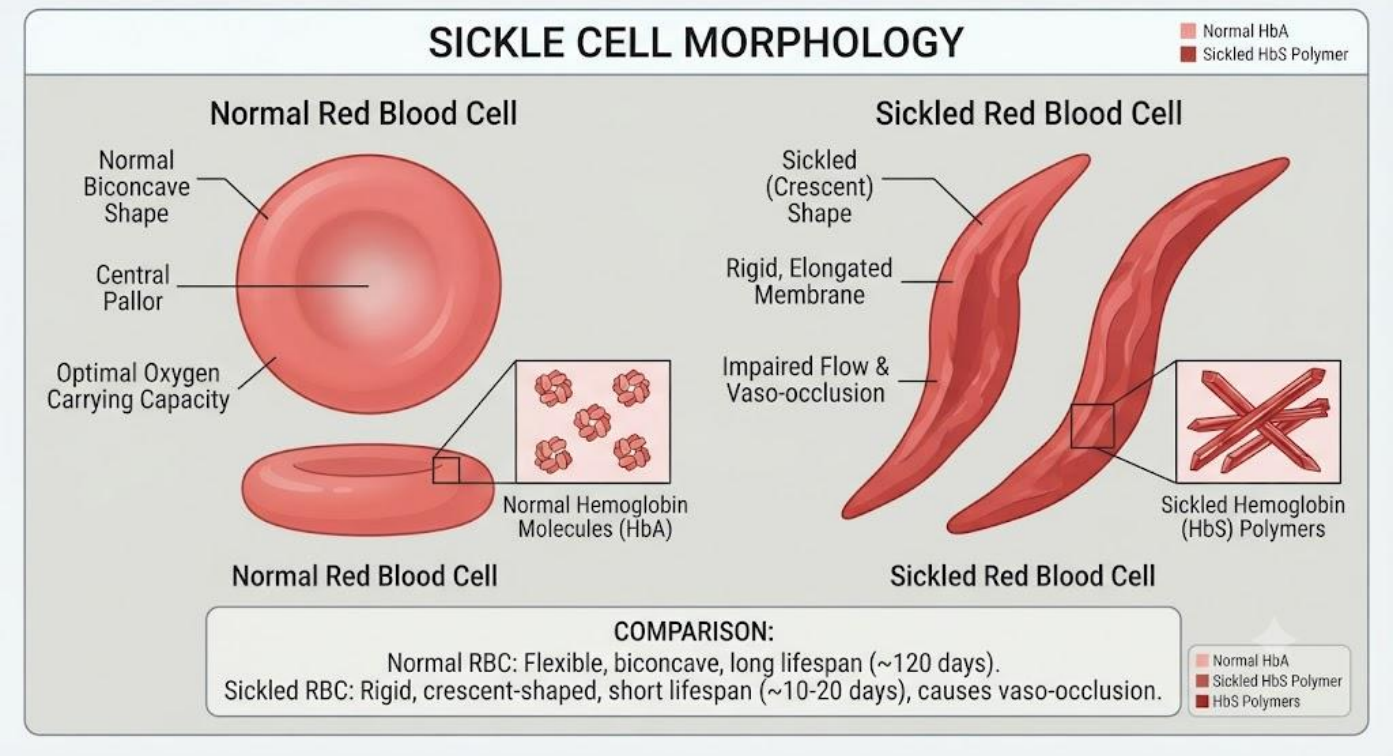

Figure 2.2: A labelled diagram comparing a normal red blood cell with a sickled cell.

Pilot questions 2.3

1. Describe the genetic basis of sickle cell disease. (Linked to SLO 2.5)
2. Distinguish sickle cell trait from sickle cell disease. (Linked to SLO 2.5)
3. Describe vaso-occlusive crisis. (Linked to SLO 2.5)
4. Describe acute chest syndrome. (Linked to SLO 2.5)
5. Describe the role of hydroxyurea in managing sickle cell disease. (Linked to SLO 2.6)

2.4 Thalassaemia

2.4.1 pathophysiology and genetics of thalassaemia

Reduced globin chain production, rather than an abnormal structure

Thalassaemia, resulting from reduced or absent production of one or more globin chains rather than the structurally abnormal haemoglobin already discussed for sickle cell disease, is classified as **alpha thalassaemia**, affecting the alpha-globin chain, or **beta thalassaemia**, affecting the beta-globin chain, with the specific clinical severity depending on how many of the relevant genes are affected in each specific case.

Beta thalassaemia major, resulting from severe deficiency of beta-globin production, produces a genuinely severe clinical syndrome requiring lifelong management discussed further later in this Part, while **beta thalassaemia minor**, the heterozygous carrier state, is generally asymptomatic, producing only mild microcytic anaemia, a genuinely important distinction paralleling the trait-versus-disease distinction already established for sickle cell disease in the previous Part.

Fill in the blank: Thalassaemia results from reduced or absent production of one or more globin _____ rather than a structurally abnormal haemoglobin.

2.4.2 clinical presentation of thalassaemia

Severe anaemia and the consequences of compensatory marrow expansion

Beta thalassaemia major presents in infancy with severe anaemia, failure to thrive, and, given the body's genuinely dramatic compensatory expansion of haematopoiesis in response to the severe underlying anaemia, characteristic skeletal changes including frontal bossing and

maxillary overgrowth, producing a genuinely recognisable facial appearance sometimes described using a specific descriptive term reflecting this compensatory bone marrow expansion.

Iron overload, resulting from both increased intestinal iron absorption driven by the underlying anaemia and, genuinely importantly, the cumulative effect of the repeated blood transfusions this condition's management requires, discussed in the following sub-Part, produces progressive organ damage, particularly affecting the heart, liver, and endocrine glands, if not actively, proactively managed alongside the underlying anaemia itself.

Fill in the blank: Iron overload in thalassaemia results from increased intestinal absorption and the cumulative effect of repeated blood _____.

2.4.3 management of thalassaemia

Regular transfusion, balanced against the genuine risk of iron overload

Regular blood transfusion, maintaining an adequate haemoglobin level and suppressing the ineffective, compensatory native erythropoiesis already discussed, forms the mainstay of management for beta thalassaemia major, and this lifelong transfusion requirement directly necessitates the **iron chelation therapy** discussed next, given the genuine, otherwise inevitable consequence of progressive iron overload this repeated transfusion produces.

Iron chelation therapy, removing excess iron before it produces genuinely significant organ damage, is genuinely essential alongside regular transfusion, and **haematopoietic stem cell transplantation**, already discussed for aplastic anaemia earlier in this Series, offers a genuinely curative option for appropriately selected patients, closing this Series on the same theme of matching treatment intensity to genuine disease severity that has run consistently throughout this course.

Fill in the blank: Iron chelation therapy removes excess iron before it produces genuinely significant organ _____.

Table 2.2: Comparing alpha and beta thalassaemia

Feature	Alpha thalassaemia	Beta thalassaemia
Globin chain affected	Alpha	Beta
Gene number involved	Four genes, variable severity	Two genes, variable severity
Most severe form	Hydrops fetalis	Beta thalassaemia major

Pilot questions 2.4

1. Distinguish alpha from beta thalassaemia. (Linked to SLO 2.7)
2. Distinguish beta thalassaemia major from beta thalassaemia minor. (Linked to SLO 2.7)
3. Describe the characteristic skeletal changes of beta thalassaemia major. (Linked to SLO 2.7)
4. Explain why iron overload develops in thalassaemia major. (Linked to SLO 2.7)
5. Describe the management of beta thalassaemia major. (Linked to SLO 2.8)

Series Summary

This Series covered aplastic anaemia and the two major haemoglobinopathies. Part 2.1 covered the pathophysiology, causes, and presentation of aplastic anaemia, while Part 2.2 turned to its investigation, management, prognosis, and complications. Part 2.3 covered sickle cell disease, and Part 2.4 closed with thalassaemia.

You should now be able to describe and manage aplastic anaemia, sickle cell disease, and thalassaemia across all four Parts of this Series, meeting the outcomes set for this Series. Series 3 turns next to bleeding disorders and haematological manifestations of chronic disease.

Glossary of Terms

1. **Acute chest syndrome:** a serious pulmonary complication of sickle cell disease.
2. **Aplastic anaemia:** bone marrow stem cell failure producing pancytopenia.
3. **Beta thalassaemia major:** severe beta-globin deficiency requiring lifelong transfusion support.
4. **Haemoglobin S:** the abnormal haemoglobin variant underlying sickle cell disease.
5. **Hydroxyurea:** medication increasing fetal haemoglobin to reduce sickle cell crises.
6. **Hypocellular marrow:** markedly reduced haematopoietic cells relative to fat content, seen in aplastic anaemia.
7. **Iron chelation therapy:** treatment removing excess iron to prevent transfusion-related organ damage.
8. **Neutropenia:** deficient neutrophil white cells, predisposing to infection.
9. **Pancytopenia:** reduction in all three major blood cell lineages.
10. **Thalassaemia:** reduced or absent globin chain production causing anaemia.

11. **Thrombocytopenia:** deficient platelets, predisposing to bleeding.
12. **Vaso-occlusive crisis:** acute, severe pain from sickled cells obstructing small blood vessels.

Concept Check Questions [Series 2]

Objective questions

- Aplastic anaemia produces pancytopenia, a reduction in all three major blood cell _____. (Linked to SLO 2.1)
- Bone marrow biopsy demonstrates a hypocellular marrow, markedly reduced haematopoietic cells relative to fat _____. (Linked to SLO 2.3)
- Sickle cell disease results from a single amino acid substitution in the beta-globin chain producing haemoglobin _____. (Linked to SLO 2.5)
- Thalassaemia results from reduced or absent production of one or more globin _____ rather than a structurally abnormal haemoglobin. (Linked to SLO 2.7)
- Iron chelation therapy removes excess iron before it produces genuinely significant organ _____. (Linked to SLO 2.8)

Short-answer questions

1. List acquired and inherited causes of aplastic anaemia. (Linked to SLO 2.1)
2. Describe stem cell transplantation as a treatment for aplastic anaemia. (Linked to SLO 2.3)
3. Distinguish sickle cell trait from sickle cell disease. (Linked to SLO 2.5)
4. Describe acute chest syndrome. (Linked to SLO 2.5)
5. Distinguish beta thalassaemia major from beta thalassaemia minor. (Linked to SLO 2.7)

Long-answer questions

6. Discuss the pathophysiology, causes, and presentation of aplastic anaemia. (Linked to SLO 2.1, 2.2)
7. Describe the investigation, management, prognosis, and complications of aplastic anaemia. (Linked to SLO 2.3, 2.4)
8. Discuss the pathophysiology, genetics, presentation, and management of sickle cell disease. (Linked to SLO 2.5, 2.6)
9. Describe the pathophysiology, genetics, and presentation of thalassaemia. (Linked to SLO 2.7)
10. Discuss the management of thalassaemia. (Linked to SLO 2.8)

Answers to Concept Check Questions [Series 2]

Objective questions

11. Lineages.
12. Content.
13. S.
14. Chains.
15. Damage.

Short-answer questions

16. Acquired causes include medications, viral infection, and radiation; inherited causes include Fanconi anaemia.
17. Transplantation replaces failed marrow with donor stem cells, offering genuine cure for suitable patients.
18. Sickle cell trait is generally asymptomatic, while sickle cell disease produces the full clinical syndrome.
19. Acute chest syndrome is a serious pulmonary complication with chest pain, breathlessness, and pulmonary infiltrate.
20. Beta thalassaemia major is severe and requires lifelong management, while minor is generally asymptomatic with mild anaemia.

Long-answer questions

21. **Basic response:** Aplastic anaemia results from stem cell failure producing pancytopenia; causes include medications, infection, and inherited conditions, though many cases are idiopathic; presentation combines anaemia, infection, and bleeding symptoms.

    Value-added response: A value-added response notes that identifying a specific causative agent carries direct management relevance through discontinuation.

22. **Basic response:** Diagnosis uses full blood count and bone marrow biopsy showing hypocellular marrow; management uses stem cell transplantation or immunosuppressive therapy; supportive care remains essential throughout.

    Value-added response: A value-added response notes that modern treatment has meaningfully improved outcomes compared with historical, untreated prognosis.

23. **Basic response:** Sickle cell disease results from an autosomal recessive haemoglobin S mutation, presenting with vaso-occlusive crisis, acute chest syndrome, and stroke; management includes acute crisis treatment and hydroxyurea.

    Value-added response: A value-added response notes that functional hyposplenism increases susceptibility to specific bacterial infections.

24. **Basic response:** Thalassaemia results from reduced globin chain production, classified as alpha or beta; beta thalassaemia major presents with severe anaemia and characteristic skeletal changes from compensatory marrow expansion.

    Value-added response: A value-added response notes that carrier states, thalassaemia minor, are generally asymptomatic with mild anaemia.

25. **Basic response:** Management centres on regular blood transfusion with iron chelation therapy to prevent overload, with stem cell transplantation offering a curative option for appropriately selected patients.

    Value-added response: A value-added response notes that iron overload from repeated transfusion directly necessitates chelation therapy.

Answers to Pilot Questions [Series 2]

Part 2.1

1. Pancytopenia is a reduction in red cells, white cells, and platelets simultaneously.
2. Aplastic anaemia most commonly involves autoimmune destruction of haematopoietic stem cells.
3. Acquired causes include medications and viral infection; inherited causes include Fanconi anaemia.
4. Discontinuing an implicated medication represents an essential, immediate first management step.
5. The pattern combines anaemia symptoms with infection from neutropenia and bleeding from thrombocytopenia.

Part 2.2

6. Investigations include full blood count, reticulocyte count, and bone marrow biopsy.

7. Excluding alternatives ensures the correct, genuinely different management approach is applied.
8. Transplantation replaces failed marrow with healthy donor stem cells, offering genuine cure.
9. Immunosuppressive therapy combines antithymocyte globulin and ciclosporin, suppressing the autoimmune process.
10. Supportive care includes transfusion support and prompt treatment of infection.

Part 2.3

11. Sickle cell disease is autosomal recessive, from a beta-globin amino acid substitution producing haemoglobin S.
12. Trait is the heterozygous, generally asymptomatic carrier state; disease is the homozygous, symptomatic state.
13. Vaso-occlusive crisis is acute, severe pain from sickled cells obstructing small blood vessels.
14. Acute chest syndrome presents with chest pain, breathlessness, and new pulmonary infiltrate.
15. Hydroxyurea increases fetal haemoglobin, reducing the frequency of vaso-occlusive crises.

Part 2.4

1. Alpha thalassaemia affects the alpha-globin chain, while beta thalassaemia affects the beta-globin chain.
2. Major is severe, requiring lifelong management, while minor is generally asymptomatic with mild anaemia.
3. Changes include frontal bossing and maxillary overgrowth from compensatory marrow expansion.
4. Iron overload results from increased intestinal absorption and cumulative transfusion iron.
5. Management centres on regular transfusion with iron chelation, with transplantation offering a curative option.

References and Attributions [Series 2]

1. Hoffbrand, A. V., & Steensma, D. P. (2019). Hoffbrand's Essential Haematology (8th ed.). Wiley-Blackwell.
2. Kumar, P., & Clark, M. (2020). Kumar and Clark's Clinical Medicine (10th ed.). Elsevier.
3. British Society for Haematology (2016). Guideline for the Diagnosis and Management of Adult Aplastic Anaemia. British Journal of Haematology.
4. National Institute for Health and Care Excellence (2012). Sickle Cell Disease: Managing Acute Painful Episodes in Hospital (CG143). NICE.

Figures, Plates, Tables, and Boxes

1. Figure 2.1: Petechiae and bruising on the forearm reflecting thrombocytopenia. AI-generated using the prompt: "Create a realistic clinical illustration titled Petechiae and Bruising, showing a close-up view of a patient's forearm with scattered small red-purple spots and areas of bruising, clean neutral background. Clean clinical illustration style, no text."
2. Table 2.1: Comparing transplantation and immunosuppressive therapy for aplastic anaemia. AI-generated using the prompt: "Create a clean reference table titled Comparing Transplantation and Immunosuppressive Therapy for Aplastic Anaemia, listing feature, stem cell transplantation, and immunosuppressive therapy. Simple clinical reference table style with outside border."
3. Figure 2.2: A labelled diagram comparing a normal red blood cell with a sickled cell. AI-generated using the prompt: "Create a clean, accurate labelled educational diagram titled Sickle Cell Morphology, showing a normal biconcave red blood cell beside a sickled, crescent-shaped red blood cell, both clearly labelled. Educational anatomical diagram style, no photographic content."
4. Table 2.2: Comparing alpha and beta thalassaemia. AI-generated using the prompt: "Create a clean reference table titled Comparing Alpha and Beta Thalassaemia, listing feature, alpha thalassaemia, and beta thalassaemia. Simple clinical reference table style with outside border."

Course code: MED 612

Course title: Haematology II

Course credit load: 2 Units

Series 3: Bleeding Disorders and Haematological Manifestations of Chronic Disease

- **Part 3.1: Approach to Bleeding Disorders**
    - Sub Part 3.1.1: Normal haemostasis
    - Sub Part 3.1.2: Classification and clinical assessment of bleeding disorders
    - Sub Part 3.1.3: Investigation of bleeding disorders
- **Part 3.2: Inherited Bleeding Disorders**
    - Sub Part 3.2.1: Haemophilia A and B
    - Sub Part 3.2.2: Von Willebrand disease
    - Sub Part 3.2.3: Management of inherited bleeding disorders
- **Part 3.3: Acquired Bleeding Disorders**
    - Sub Part 3.3.1: Thrombocytopenia
    - Sub Part 3.3.2: Disseminated intravascular coagulation
    - Sub Part 3.3.3: Anticoagulant-related bleeding
- **Part 3.4: Haematological Manifestations of Chronic Disease**
    - Sub Part 3.4.1: Anaemia of chronic disease
    - Sub Part 3.4.2: Haematological manifestations of chronic kidney disease
    - Sub Part 3.4.3: Haematological manifestations of chronic liver disease

Introduction

This Series turns to **bleeding disorders**, spanning both inherited and acquired causes of abnormal haemostasis, before closing with the **haematological manifestations of chronic disease**, the genuinely wide-ranging effects that chronic illness elsewhere in the body can produce on the blood itself. Both topics demand a genuinely structured, systematic approach given the wide differential each presents, building directly on the anaemia framework already established in Series 1 of this course.

The aim of this Series is to equip you with an understanding of normal haemostasis and the classification, assessment, and investigation of bleeding disorders, the inherited bleeding disorders of haemophilia A and B and von Willebrand disease and their management, the acquired bleeding disorders of thrombocytopenia, disseminated intravascular coagulation, and anticoagulant-related bleeding, and the haematological manifestations of chronic disease, including anaemia of chronic disease and the effects of chronic kidney and liver disease.

This Series opens with the **approach to bleeding disorders**, moves through **inherited bleeding disorders** and **acquired bleeding disorders**, and closes with **haematological manifestations of chronic disease**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 3.1:** describe normal haemostasis and the classification of bleeding disorders
- **SLO 3.2:** describe the clinical assessment and investigation of bleeding disorders
- **SLO 3.3:** describe haemophilia A and B and von Willebrand disease
- **SLO 3.4:** discuss the management of inherited bleeding disorders
- **SLO 3.5:** describe thrombocytopenia and disseminated intravascular coagulation
- **SLO 3.6:** discuss anticoagulant-related bleeding
- **SLO 3.7:** describe anaemia of chronic disease
- **SLO 3.8:** describe the haematological manifestations of chronic kidney and liver disease

3.1 Approach to Bleeding Disorders

3.1.1 normal haemostasis

A genuinely coordinated, sequential physiological process

Normal **haemostasis** proceeds through **primary haemostasis**, platelets adhering to and aggregating at a site of vessel injury to form an initial platelet plug, and **secondary haemostasis**, the **coagulation cascade**, a sequential series of enzymatic reactions ultimately converting fibrinogen to fibrin, stabilising the initial platelet plug into a genuinely robust, durable clot capable of withstanding ongoing blood flow.

The coagulation cascade proceeds through **intrinsic**, **extrinsic**, and **common** pathways, converging on the activation of factor X and, ultimately, thrombin generation, and understanding this specific pathway structure directly explains the pattern of laboratory test abnormalities produced by deficiency of a specific individual clotting factor, discussed further in the following two Parts of this Series.

Fill in the blank: Secondary haemostasis, the coagulation cascade, ultimately converts fibrinogen to _____.

3.1.2 classification and clinical assessment of bleeding disorders

Distinguishing platelet-type from coagulation factor-type bleeding

Bleeding disorders are broadly classified as disorders of **primary haemostasis**, platelet number or function, presenting characteristically with mucocutaneous bleeding, petechiae, easy bruising, and epistaxis, or disorders of **secondary haemostasis**, coagulation factor deficiency, presenting characteristically with deep tissue bleeding, haemarthrosis, joint bleeding, and muscle haematoma, a genuinely useful clinical distinction directly guiding the subsequent differential diagnosis and investigation pathway.

A thorough bleeding history, including the specific pattern of bleeding already discussed, family history given the genuine relevance of inherited bleeding disorders discussed in the following Part, and specific bleeding challenges such as excessive bleeding following dental extraction or surgery, provides genuinely valuable diagnostic information before any laboratory investigation, discussed in the following sub-Part, is even performed.

Fill in the blank: Disorders of secondary haemostasis present characteristically with deep tissue bleeding and haemarthrosis, joint _____.

3.1.3 investigation of bleeding disorders

A structured panel confirming and localising the specific defect

Full blood count, including platelet count, alongside **prothrombin time**, assessing the extrinsic and common coagulation pathways, and **activated partial thromboplastin time**, assessing the intrinsic and common pathways, form the essential initial investigation panel for any suspected bleeding disorder, with the specific pattern of abnormality across these tests genuinely narrowing the differential diagnosis considerably before further specific testing is pursued.

Where these initial tests suggest a specific coagulation pathway abnormality, **specific clotting factor assays**, directly measuring individual factor levels, confirm the precise underlying deficiency, and this genuinely structured, stepwise investigation approach, moving from broad screening tests to increasingly specific confirmatory testing, reflects the same systematic diagnostic philosophy already emphasised throughout this course.

Fill in the blank: Specific clotting factor assays directly measure individual factor levels to confirm the precise underlying _____.

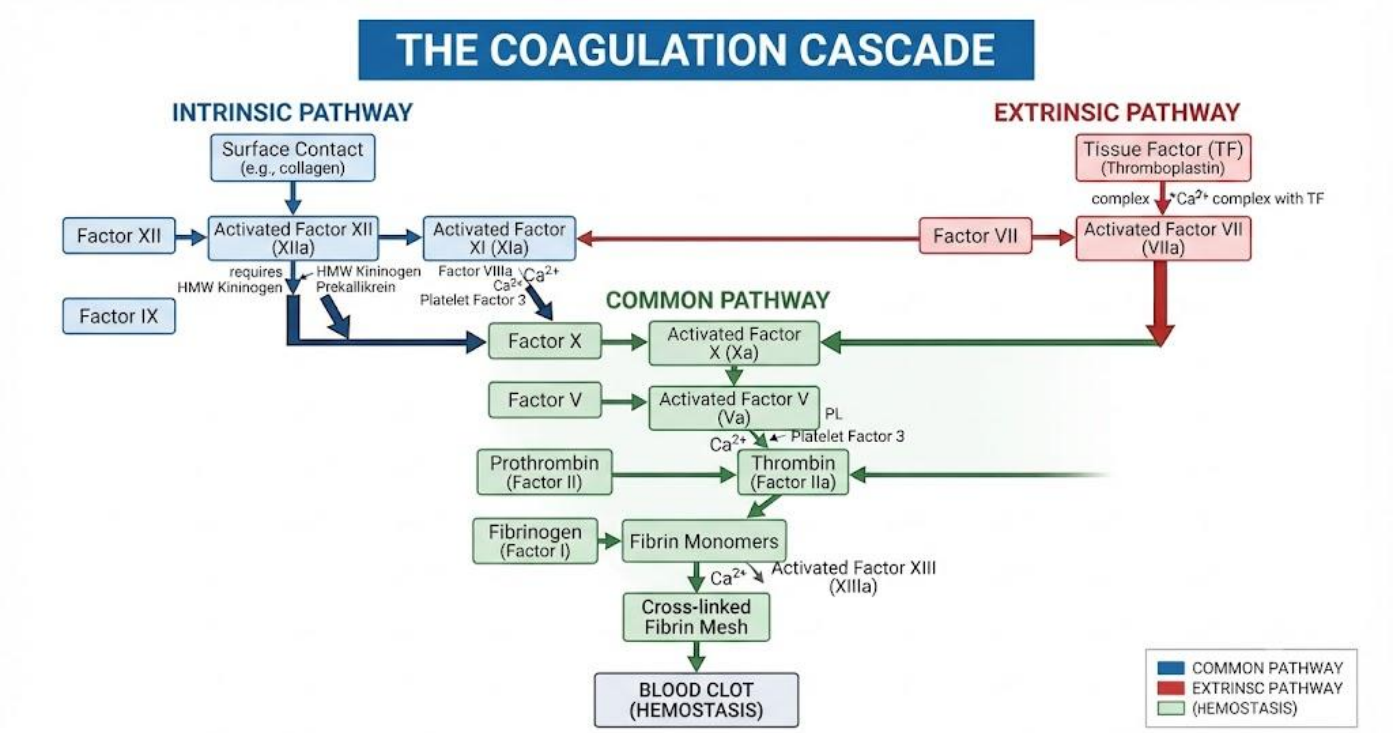

Figure 3.1: A labelled diagram of the coagulation cascade showing the intrinsic, extrinsic, and common pathways.

Pilot questions 3.1

- Distinguish primary from secondary haemostasis. (Linked to SLO 3.1)
- Describe the intrinsic, extrinsic, and common coagulation pathways. (Linked to SLO 3.1)
- Distinguish the bleeding pattern of primary haemostasis disorders from secondary haemostasis disorders. (Linked to SLO 3.2)
- List key elements of a bleeding history. (Linked to SLO 3.2)
- Describe the initial investigation panel for a suspected bleeding disorder. (Linked to SLO 3.2)

3.2 Inherited Bleeding Disorders

3.2.1 haemophilia a and b

X-linked deficiency of a specific clotting factor

Haemophilia A, deficiency of clotting factor VIII, and **haemophilia B**, deficiency of clotting factor IX, both X-linked recessive conditions predominantly affecting males, present with the characteristic secondary haemostasis bleeding pattern already discussed in the previous Part, haemarthrosis and deep tissue bleeding, with severity, mild, moderate, or severe, genuinely correlating with the specific residual factor level the affected individual retains.

Recurrent haemarthrosis, if inadequately treated, produces progressive, genuinely irreversible joint damage termed **haemophilic arthropathy**, underlining why prompt, effective treatment of individual bleeding episodes, discussed further later in this Part, genuinely matters beyond simply managing the acute episode, given its direct relevance to long-term joint function and quality of life for affected individuals.

Fill in the blank: Haemophilia A is deficiency of clotting factor _____.

3.2.2 von willebrand disease

The most common inherited bleeding disorder overall

Von Willebrand disease, the most common inherited bleeding disorder overall, results from deficiency or dysfunction of **von Willebrand factor**, a protein genuinely essential for both normal platelet adhesion and stabilisation of factor VIII in the circulation, meaning this single

deficiency can produce a genuinely combined bleeding pattern reflecting both primary and secondary haemostasis dysfunction simultaneously.

Presentation typically reflects the primary haemostasis pattern already discussed, mucocutaneous bleeding and easy bruising, often genuinely milder than haemophilia given the typically partial, rather than complete, deficiency this condition produces, and von Willebrand disease is classified into several distinct subtypes reflecting differing degrees and mechanisms of von Willebrand factor deficiency or dysfunction, each carrying specific management implications.

Fill in the blank: Von Willebrand factor is genuinely essential for both normal platelet adhesion and stabilisation of factor _____ in the circulation.

3.2.3 management of inherited bleeding disorders

Replacing the deficient factor, promptly and appropriately

Factor replacement therapy, administering the specific deficient clotting factor intravenously, either on demand during an acute bleeding episode or as regular prophylaxis to prevent bleeding episodes before they occur, forms the mainstay of haemophilia management, with prophylactic treatment increasingly preferred given its genuine, meaningful reduction in the long-term joint damage already discussed in relation to haemophilic arthropathy.

Desmopressin, stimulating release of stored von Willebrand factor and factor VIII, offers effective treatment for mild haemophilia A and many cases of von Willebrand disease, avoiding the need for factor concentrate in appropriately selected patients, and comprehensive care, including genuine patient education about bleeding recognition and management, forms an essential, ongoing component of care for any patient with an inherited bleeding disorder.

Fill in the blank: Desmopressin stimulates release of stored von Willebrand factor and factor _____.

Table 3.1: Comparing haemophilia A, haemophilia B, and von Willebrand disease

Condition	Deficient factor	Typical bleeding pattern
Haemophilia A	Factor VIII	Haemarthrosis, deep tissue bleeding
Haemophilia B	Factor IX	Haemarthrosis, deep tissue bleeding
Von Willebrand disease	Von Willebrand factor	Mucocutaneous bleeding, easy bruising

Pilot questions 3.2

1. Distinguish haemophilia A from haemophilia B. (Linked to SLO 3.3)
2. Describe haemophilic arthropathy. (Linked to SLO 3.3)
3. Describe von Willebrand disease and its underlying mechanism. (Linked to SLO 3.3)
4. Describe factor replacement therapy. (Linked to SLO 3.4)
5. Describe the role of desmopressin in managing inherited bleeding disorders. (Linked to SLO 3.4)

3.3 Acquired Bleeding Disorders

3.3.1 thrombocytopenia

Reduced platelet number, from a genuinely wide range of causes

Thrombocytopenia, a reduced platelet count, already introduced in the context of aplastic anaemia in Series 2, results from reduced platelet production, including bone marrow failure or infiltration, increased platelet destruction, including immune thrombocytopenia, an autoimmune condition directly targeting platelets, or increased platelet consumption, including disseminated intravascular coagulation discussed in the following sub-Part.

Immune thrombocytopenia, resulting from autoantibodies directed against platelets, presents with the characteristic primary haemostasis bleeding pattern already discussed, and management ranges from observation for genuinely mild, asymptomatic cases, to corticosteroid therapy or, for refractory cases, other specific treatment approaches, chosen according to the severity of thrombocytopenia and the genuine bleeding risk it produces for the individual patient.

Fill in the blank: Immune thrombocytopenia results from autoantibodies directed against _____.

3.3.2 disseminated intravascular coagulation

A genuine emergency of simultaneous clotting and bleeding

Disseminated intravascular coagulation, a genuine medical emergency resulting from widespread, inappropriate activation of the coagulation cascade, most commonly triggered by

sepsis, severe trauma, or obstetric complications, consumes both clotting factors and platelets faster than the body can replace them, producing the genuinely paradoxical combination of widespread microvascular thrombosis and, simultaneously, significant bleeding as clotting resources become depleted.

Diagnosis combines the clinical context of a recognised triggering condition with characteristic laboratory findings, including thrombocytopenia, prolonged coagulation times, low fibrinogen, and elevated **D-dimer**, already discussed in relation to venous thromboembolism in an earlier course of this programme, reflecting genuinely widespread clot formation and breakdown occurring simultaneously, and management centres on treating the underlying triggering condition alongside supportive replacement of consumed clotting factors and platelets.

Fill in the blank: Disseminated intravascular coagulation produces the genuinely paradoxical combination of widespread microvascular thrombosis and simultaneous _____.

3.3.3 anticoagulant-related bleeding

A genuinely important, entirely iatrogenic cause of bleeding

Anticoagulant medication, prescribed for conditions including atrial fibrillation and venous thromboembolism already discussed in earlier courses of this programme, carries an inherent, genuinely expected trade-off of increased bleeding risk, and recognising anticoagulant-related bleeding, whether minor or genuinely life-threatening, requires active consideration in any patient on anticoagulant therapy presenting with unexplained bleeding or a significant drop in haemoglobin.

Reversal agents, specific to the particular anticoagulant class involved, allow urgent correction of anticoagulation in significant, life-threatening bleeding, and, alongside general supportive measures already discussed for other bleeding disorders in this Series, the decision to reverse anticoagulation genuinely requires weighing the immediate bleeding risk against the competing thrombotic risk the anticoagulant was originally prescribed to prevent, a genuinely individualised clinical judgement closing this Part's coverage.

Fill in the blank: Reversal agents are specific to the particular anticoagulant class involved, allowing urgent correction of _____ in significant bleeding.

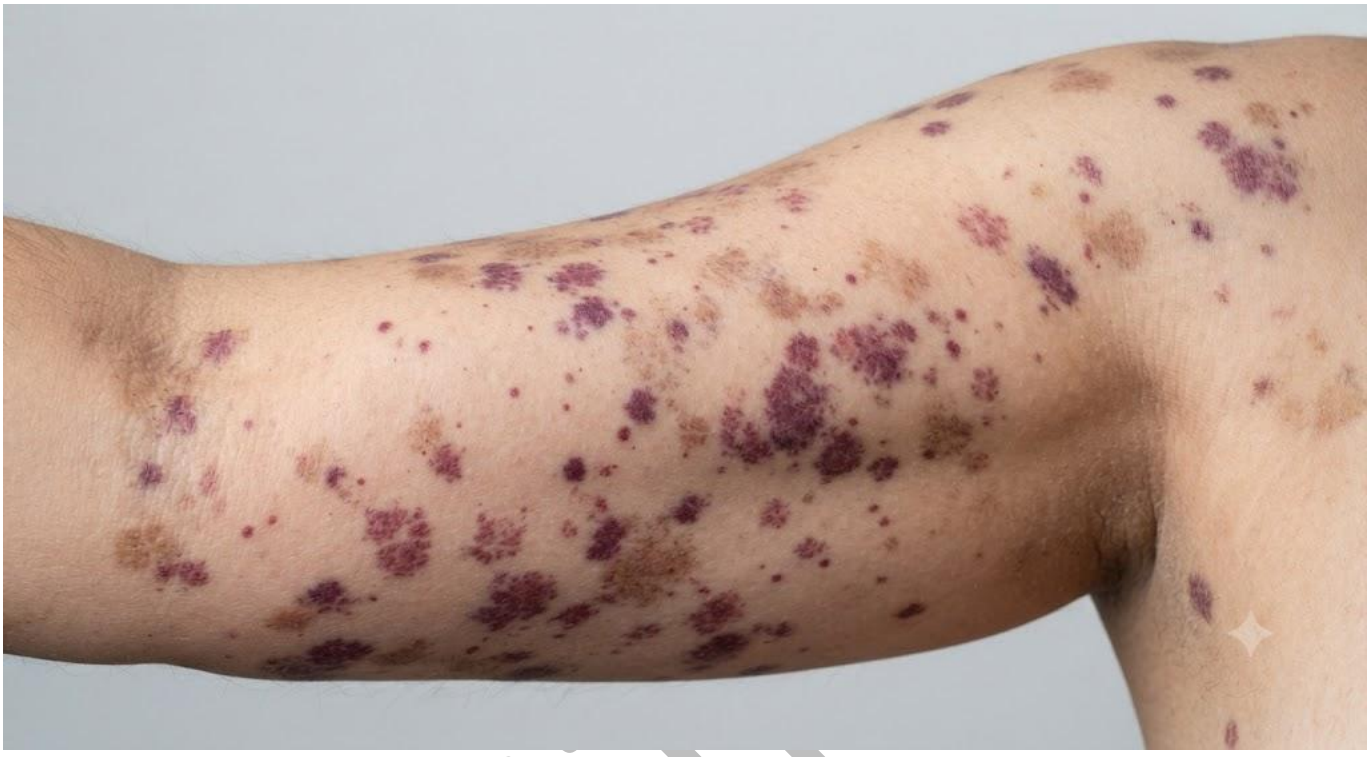

Figure 3.2: Widespread purpura reflecting significant bleeding tendency.

Pilot questions 3.3

1. Describe the causes of thrombocytopenia. (Linked to SLO 3.5)
2. Describe immune thrombocytopenia. (Linked to SLO 3.5)
3. Describe disseminated intravascular coagulation and its typical triggers. (Linked to SLO 3.5)
4. List the characteristic laboratory findings of disseminated intravascular coagulation. (Linked to SLO 3.5)
5. Describe the approach to managing significant anticoagulant-related bleeding. (Linked to SLO 3.6)

3.4 Haematological Manifestations of Chronic Disease

3.4.1 anaemia of chronic disease

A genuinely distinct mechanism from the nutritional anaemias

Anaemia of chronic disease, resulting from chronic inflammation disrupting normal iron utilisation and erythropoiesis, is genuinely one of the most common causes of normocytic

anaemia already introduced in the classification framework established in Series 1 of this course, occurring in association with a genuinely wide range of chronic conditions, including chronic infection, inflammatory disease already discussed in an earlier course of this programme, and malignancy.

Distinguishing anaemia of chronic disease from iron deficiency anaemia already discussed in Series 1, since both can produce a genuinely similar biochemical picture, particularly a low serum iron, relies on specific iron study patterns, with ferritin typically normal or elevated in anaemia of chronic disease, reflecting adequate iron stores that the underlying inflammatory process is genuinely preventing from being effectively utilised, in contrast to the genuinely low ferritin characteristic of true iron deficiency.

Fill in the blank: Ferritin is typically normal or elevated in anaemia of chronic disease, reflecting adequate iron _____ that cannot be effectively utilised.

3.4.2 haematological manifestations of chronic kidney disease

Reduced erythropoietin production, and its downstream consequences

Chronic kidney disease, already discussed in an earlier course of this programme, produces anaemia primarily through reduced renal **erythropoietin** production, the hormone genuinely essential for stimulating red cell production within the bone marrow, and this specific, well-characterised mechanism directly explains why anaemia genuinely worsens as kidney function progressively declines, and why erythropoietin replacement, discussed further next, offers a genuinely targeted treatment approach.

Erythropoiesis-stimulating agents, replacing the deficient endogenous erythropoietin, alongside iron supplementation given the genuine relevance of adequate iron availability to effective erythropoiesis, form the mainstay of managing chronic kidney disease-related anaemia, and chronic kidney disease can also genuinely affect platelet function, contributing to a bleeding tendency despite a genuinely normal platelet count in many affected patients.

Fill in the blank: Erythropoiesis-stimulating agents replace the deficient endogenous _____ in chronic kidney disease.

3.4.3 haematological manifestations of chronic liver disease

Reduced clotting factor synthesis and genuine platelet sequestration

Chronic liver disease, already discussed in genuine depth in an earlier course of this programme, produces haematological effects through several genuinely distinct mechanisms,

including reduced hepatic synthesis of most clotting factors, producing a genuine bleeding tendency, and **hypersplenism**, splenic enlargement from portal hypertension already discussed in that earlier course, causing platelet sequestration and consequent thrombocytopenia.

Coagulopathy in chronic liver disease genuinely requires careful, nuanced interpretation, since reduced production of both procoagulant and anticoagulant factors can produce a genuinely complex, sometimes paradoxically thrombosis-prone rather than purely bleeding-prone overall haemostatic balance, meaning standard coagulation tests alone should never be used in isolation to definitively predict either bleeding or clotting risk in this specific patient population, closing this Series on a genuinely important note of interpretive caution.

Fill in the blank: Hypersplenism causes platelet sequestration and consequent _____ in chronic liver disease.

Table 3.2: Comparing haematological manifestations of chronic kidney disease and chronic liver disease

Feature	Chronic kidney disease	Chronic liver disease
Primary mechanism	Reduced erythropoietin production	Reduced clotting factor synthesis, hypersplenism
Key haematological effect	Anaemia	Anaemia, thrombocytopenia, coagulopathy
Key management approach	Erythropoiesis-stimulating agents	Address underlying liver disease, supportive care

Pilot questions 3.4

1. Describe anaemia of chronic disease and its underlying mechanism. (Linked to SLO 3.7)
2. Distinguish anaemia of chronic disease from iron deficiency anaemia using ferritin. (Linked to SLO 3.7)
3. Describe the mechanism of anaemia in chronic kidney disease. (Linked to SLO 3.8)
4. Describe the haematological effects of chronic liver disease. (Linked to SLO 3.8)
5. Explain why standard coagulation tests should not be used alone to predict bleeding or clotting risk in liver disease. (Linked to SLO 3.8)

Series Summary

This Series covered bleeding disorders and the haematological manifestations of chronic disease. Part 3.1 covered normal haemostasis and the classification and investigation of bleeding disorders, while Part 3.2 turned to the inherited bleeding disorders. Part 3.3 covered the acquired bleeding disorders, and Part 3.4 closed with the haematological manifestations of chronic disease, chronic kidney disease, and chronic liver disease.

You should now be able to assess, investigate, and manage bleeding disorders and describe the haematological manifestations of chronic disease across all four Parts of this Series, meeting the outcomes set for this Series. Series 4 turns next to myeloproliferative disorders and leukaemias.

Glossary of Terms

1. **Anaemia of chronic disease:** anaemia from chronic inflammation disrupting iron utilisation and erythropoiesis.
2. **Coagulation cascade:** the sequential enzymatic reactions of secondary haemostasis converting fibrinogen to fibrin.
3. **Disseminated intravascular coagulation:** widespread, inappropriate coagulation activation causing simultaneous clotting and bleeding.
4. **Erythropoietin:** a hormone stimulating red cell production, deficient in chronic kidney disease.
5. **Haemarthrosis:** bleeding into a joint, characteristic of secondary haemostasis disorders.
6. **Haemophilia A:** deficiency of clotting factor VIII.
7. **Haemophilia B:** deficiency of clotting factor IX.
8. **Hypersplenism:** splenic enlargement causing platelet sequestration and thrombocytopenia.
9. **Immune thrombocytopenia:** autoimmune destruction of platelets by autoantibodies.
10. **Primary haemostasis:** platelet adhesion and aggregation forming the initial platelet plug.
11. **Thrombocytopenia:** a reduced platelet count from reduced production, increased destruction, or consumption.
12. **Von Willebrand disease:** the most common inherited bleeding disorder, from von Willebrand factor deficiency.

Concept Check Questions [Series 3]

Objective questions

- Secondary haemostasis, the coagulation cascade, ultimately converts fibrinogen to _____. (Linked to SLO 3.1)
- Haemophilia A is deficiency of clotting factor _____. (Linked to SLO 3.3)
- Disseminated intravascular coagulation produces the genuinely paradoxical combination of widespread microvascular thrombosis and simultaneous _____. (Linked to SLO 3.5)
- Ferritin is typically normal or elevated in anaemia of chronic disease, reflecting adequate iron _____ that cannot be effectively utilised. (Linked to SLO 3.7)
- Hypersplenism causes platelet sequestration and consequent _____ in chronic liver disease. (Linked to SLO 3.8)

Short-answer questions

1. Distinguish the bleeding pattern of primary haemostasis disorders from secondary haemostasis disorders. (Linked to SLO 3.2)
2. Describe von Willebrand disease and its underlying mechanism. (Linked to SLO 3.3)
3. List the characteristic laboratory findings of disseminated intravascular coagulation. (Linked to SLO 3.5)
4. Describe the mechanism of anaemia in chronic kidney disease. (Linked to SLO 3.8)
5. Describe the haematological effects of chronic liver disease. (Linked to SLO 3.8)

Long-answer questions

6. Discuss normal haemostasis and the classification, assessment, and investigation of bleeding disorders. (Linked to SLO 3.1, 3.2)
7. Describe haemophilia A and B and von Willebrand disease and their management. (Linked to SLO 3.3, 3.4)
8. Discuss thrombocytopenia, disseminated intravascular coagulation, and anticoagulant-related bleeding. (Linked to SLO 3.5, 3.6)
9. Describe anaemia of chronic disease. (Linked to SLO 3.7)
10. Discuss the haematological manifestations of chronic kidney and liver disease. (Linked to SLO 3.8)

Answers to Concept Check Questions [Series 3]

Objective questions

11. Fibrin.
12. VIII.
13. Bleeding.
14. Stores.
15. Thrombocytopenia.

Short-answer questions

16. Primary haemostasis disorders cause mucocutaneous bleeding and bruising, while secondary disorders cause deep tissue and joint bleeding.
17. Von Willebrand disease results from deficiency or dysfunction of von Willebrand factor, affecting platelet adhesion and factor VIII stability.
18. Findings include thrombocytopenia, prolonged coagulation times, low fibrinogen, and elevated D-dimer.
19. Chronic kidney disease reduces renal erythropoietin production, essential for stimulating red cell production.
20. Chronic liver disease reduces clotting factor synthesis and causes hypersplenism-related thrombocytopenia.

Long-answer questions

21. **Basic response:** Haemostasis proceeds through primary platelet plug formation and secondary coagulation cascade activation; bleeding disorders are classified by pattern, assessed through history, and investigated with full blood count and coagulation screening.

    Value-added response: A value-added response notes that specific clotting factor assays confirm the precise underlying deficiency once screening tests suggest an abnormality.

22. **Basic response:** Haemophilia A and B are X-linked factor VIII and IX deficiencies causing haemarthrosis; von Willebrand disease causes combined bleeding patterns from factor deficiency; management uses factor replacement or desmopressin.

    Value-added response: A value-added response notes that recurrent haemarthrosis without adequate treatment produces irreversible haemophilic arthropathy.

23. **Basic response:** Thrombocytopenia results from reduced production, increased destruction, or consumption; disseminated intravascular coagulation causes simultaneous

clotting and bleeding from a triggering condition; anticoagulant bleeding requires weighing reversal against thrombotic risk.

Value-added response: A value-added response notes that immune thrombocytopenia results from autoantibodies directly targeting platelets.

24. **Basic response:** Anaemia of chronic disease results from chronic inflammation disrupting iron utilisation, distinguished from iron deficiency by a typically normal or elevated ferritin.

    Value-added response: A value-added response notes this is one of the most common causes of normocytic anaemia across a wide range of chronic conditions.

25. **Basic response:** Chronic kidney disease causes anaemia through reduced erythropoietin production, managed with erythropoiesis-stimulating agents; chronic liver disease causes anaemia, thrombocytopenia, and coagulopathy through reduced clotting factor synthesis and hypersplenism.

    Value-added response: A value-added response notes that standard coagulation tests alone should never be used to definitively predict bleeding or clotting risk in liver disease.

Answers to Pilot Questions [Series 3]

Part 3.1

1. Primary haemostasis is initial platelet plug formation, while secondary haemostasis is the coagulation cascade.
2. The intrinsic and extrinsic pathways converge on the common pathway, ultimately activating thrombin.
3. Primary haemostasis disorders cause mucocutaneous bleeding, while secondary disorders cause deep tissue and joint bleeding.
4. Elements include bleeding pattern, family history, and specific challenges such as surgical bleeding.
5. The panel includes full blood count, prothrombin time, and activated partial thromboplastin time.

Part 3.2

6. Haemophilia A is factor VIII deficiency, while haemophilia B is factor IX deficiency.
7. Haemophilic arthropathy is progressive, irreversible joint damage from recurrent, inadequately treated haemarthrosis.
8. Von Willebrand disease results from deficiency or dysfunction of von Willebrand factor, affecting platelets and factor VIII.
9. Factor replacement therapy administers the deficient clotting factor intravenously, on demand or as prophylaxis.
10. Desmopressin stimulates release of stored von Willebrand factor and factor VIII, avoiding the need for factor concentrate.

Part 3.3

11. Causes include reduced production, increased destruction, and increased consumption of platelets.
12. Immune thrombocytopenia results from autoantibodies directed against platelets.
13. Disseminated intravascular coagulation is triggered by sepsis, trauma, or obstetric complications.
14. Findings include thrombocytopenia, prolonged coagulation times, low fibrinogen, and elevated D-dimer.
15. Management weighs reversal against thrombotic risk, using specific reversal agents where genuinely indicated.

Part 3.4

1. Anaemia of chronic disease results from chronic inflammation disrupting iron utilisation and erythropoiesis.
2. Ferritin is typically normal or elevated in chronic disease, unlike the low ferritin of true iron deficiency.
3. Chronic kidney disease reduces renal erythropoietin production, essential for red cell production.
4. Effects include anaemia, thrombocytopenia from hypersplenism, and coagulopathy from reduced clotting factor synthesis.
5. Reduced production of both procoagulant and anticoagulant factors creates a complex, sometimes paradoxical balance.

References and Attributions [Series 3]

1. Hoffbrand, A. V., & Steensma, D. P. (2019). Hoffbrand's Essential Haematology (8th ed.). Wiley-Blackwell.
2. Kumar, P., & Clark, M. (2020). Kumar and Clark's Clinical Medicine (10th ed.). Elsevier.
3. United Kingdom Haemophilia Centre Doctors' Organisation (2020). Guideline for the Diagnosis and Management of Haemophilia. Haemophilia.
4. British Society for Haematology (2018). Guideline for the Diagnosis and Management of Disseminated Intravascular Coagulation. British Journal of Haematology.

Figures, Plates, Tables, and Boxes

1. Figure 3.1: A labelled diagram of the coagulation cascade showing the intrinsic, extrinsic, and common pathways. AI-generated using the prompt: "Create a clean, accurate labelled educational diagram titled The Coagulation Cascade, showing the intrinsic pathway, extrinsic pathway, and common pathway converging on fibrin formation, with key clotting factors labelled at each step. Educational anatomical diagram style, no photographic content."
2. Table 3.1: Comparing haemophilia A, haemophilia B, and von Willebrand disease. AI-generated using the prompt: "Create a clean reference table titled Comparing Haemophilia A, Haemophilia B, and Von Willebrand Disease, listing condition, deficient factor, and typical bleeding pattern. Simple clinical reference table style with outside border."
3. Figure 3.2: Widespread purpura reflecting significant bleeding tendency. AI-generated using the prompt: "Create a realistic clinical illustration titled Purpura from Severe Thrombocytopenia, showing a close-up view of a patient's skin with widespread small to moderate purple-red discoloured patches, clean neutral background. Clean clinical illustration style, no text."
4. Table 3.2: Comparing haematological manifestations of chronic kidney disease and chronic liver disease. AI-generated using the prompt: "Create a clean reference table titled Comparing Haematological Manifestations of Chronic Kidney Disease and Chronic Liver Disease, listing feature, chronic kidney disease, and chronic liver disease. Simple clinical reference table style with outside border."

Course code: MED 612

Course title: Haematology II

Course credit load: 2 Units

Series 4: Myeloproliferative Disorders and Leukaemias

- **Part 4.1: Myeloproliferative Disorders**
  - Sub Part 4.1.1: Classification and pathophysiology of myeloproliferative disorders
  - Sub Part 4.1.2: Polycythaemia vera
  - Sub Part 4.1.3: Essential thrombocythaemia and primary myelofibrosis
- **Part 4.2: Chronic Myeloid Leukaemia**
  - Sub Part 4.2.1: Pathophysiology and genetics of chronic myeloid leukaemia
  - Sub Part 4.2.2: Clinical presentation and diagnosis of chronic myeloid leukaemia
  - Sub Part 4.2.3: Management of chronic myeloid leukaemia
- **Part 4.3: Acute Leukaemias**
  - Sub Part 4.3.1: Acute myeloid leukaemia
  - Sub Part 4.3.2: Acute lymphoblastic leukaemia
  - Sub Part 4.3.3: Investigation and diagnosis of acute leukaemia
- **Part 4.4: Management of Acute Leukaemia and Chronic Lymphocytic Leukaemia**
  - Sub Part 4.4.1: Management principles of acute leukaemia
  - Sub Part 4.4.2: Complications of acute leukaemia and its treatment
  - Sub Part 4.4.3: Chronic lymphocytic leukaemia

Introduction

This Series turns to genuinely proliferative haematological disease, conditions where the bone marrow produces too many, rather than too few, of one or more blood cell lineages. **Myeloproliferative disorders**, **chronic myeloid leukaemia**, and the **acute leukaemias**, alongside **chronic lymphocytic leukaemia**, each reflect a genuinely distinct underlying clonal process, and confidently distinguishing between them, and recognising their genuinely characteristic presentation, forms the core of this Series.

The aim of this Series is to equip you with an understanding of the classification and pathophysiology of myeloproliferative disorders, including polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis, the pathophysiology, genetics, presentation, diagnosis, and management of chronic myeloid leukaemia, the pathophysiology, presentation, investigation, and management of acute myeloid and acute lymphoblastic leukaemia, and the presentation of chronic lymphocytic leukaemia.

This Series opens with **myeloproliferative disorders**, moves through **chronic myeloid leukaemia** and **acute leukaemias**, and closes with **management of acute leukaemia and chronic lymphocytic leukaemia**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 4.1:** describe the classification and pathophysiology of myeloproliferative disorders
- **SLO 4.2:** describe polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis
- **SLO 4.3:** describe the pathophysiology, genetics, presentation, diagnosis, and management of chronic myeloid leukaemia
- **SLO 4.4:** describe acute myeloid leukaemia and acute lymphoblastic leukaemia
- **SLO 4.5:** discuss the investigation and diagnosis of acute leukaemia
- **SLO 4.6:** discuss the management principles of acute leukaemia
- **SLO 4.7:** describe the complications of acute leukaemia and its treatment
- **SLO 4.8:** describe chronic lymphocytic leukaemia

4.1 Myeloproliferative Disorders

4.1.1 classification and pathophysiology of myeloproliferative disorders

Clonal overproduction of one or more mature blood cell lineages

Myeloproliferative disorders, resulting from a clonal proliferation of an abnormal haematopoietic stem cell producing excess, though genuinely functionally mature, blood cells of one or more lineages, are classified according to the predominantly affected lineage: **polycythaemia vera**, predominantly red cells, **essential thrombocythaemia**, predominantly platelets, and **primary myelofibrosis**, characterised by genuine bone marrow fibrosis alongside variable overproduction of multiple lineages.

A specific acquired mutation in the **JAK2 gene**, affecting a protein genuinely central to the signalling pathway controlling blood cell production, is present in the great majority of patients with polycythaemia vera and a meaningful proportion of patients with essential thrombocythaemia and primary myelofibrosis, and this shared, though genuinely not universal, molecular abnormality directly underlies the specific diagnostic testing discussed further across this Part.

Fill in the blank: A specific acquired mutation in the _____ gene is present in the great majority of polycythaemia vera patients.

4.1.2 polycythaemia vera

Excess red cell production carrying genuine thrombotic risk

Polycythaemia vera, characterised by genuine excess red cell production, presents with symptoms including headache, dizziness, and genuinely characteristic **pruritus**, itching, particularly after a warm bath, alongside facial plethora, ruddy facial complexion, and, given the significantly increased blood viscosity this condition produces, a genuinely meaningful, elevated risk of both arterial and venous thrombosis.

Management centres on **venesection**, therapeutic blood removal, reducing red cell mass and genuinely, directly reducing thrombotic risk, alongside low-dose aspirin given the elevated thrombotic risk already discussed, and, for higher-risk patients, cytoreductive medication reducing overall blood cell production, with the specific treatment intensity genuinely individualised according to the patient's assessed thrombotic risk profile.

Fill in the blank: Polycythaemia vera presents with characteristic pruritus, itching, particularly after a warm _____.

4.1.3 essential thrombocythaemia and primary myelofibrosis

Excess platelets, and progressive marrow scarring

Essential thrombocythaemia, characterised by genuine excess platelet production, is frequently asymptomatic, identified incidentally on routine blood testing, though it carries an elevated thrombotic risk genuinely similar in principle to polycythaemia vera already discussed, and, paradoxically, can also produce bleeding tendency in some patients given genuine platelet dysfunction that can accompany the markedly elevated platelet count.

Primary myelofibrosis, the genuinely most severe myeloproliferative disorder, produces progressive bone marrow fibrosis, eventually impairing normal haematopoiesis and producing genuine cytopenias despite the disease's proliferative origin, alongside significant splenomegaly from **extramedullary haematopoiesis**, blood cell production occurring outside the fibrosed marrow, most commonly within the spleen, and carries the genuine risk of transformation to acute myeloid leukaemia, discussed further later in this Series.

Fill in the blank: Primary myelofibrosis produces significant splenomegaly from extramedullary haematopoiesis, blood cell production outside the fibrosed _____.

Figure 4.1: Facial plethora, ruddy complexion, characteristic of polycythaemia vera.

Pilot questions 4.1

- Describe the classification of myeloproliferative disorders. (Linked to SLO 4.1)
- Describe the JAK2 mutation and its relevance. (Linked to SLO 4.1)
- Describe the presentation of polycythaemia vera. (Linked to SLO 4.2)
- Describe venesection as a treatment for polycythaemia vera. (Linked to SLO 4.2)
- Describe primary myelofibrosis and extramedullary haematopoiesis. (Linked to SLO 4.2)

4.2 Chronic Myeloid Leukaemia

4.2.1 pathophysiology and genetics of chronic myeloid leukaemia

A single, genuinely defining chromosomal translocation

Chronic myeloid leukaemia, a genuinely distinct clonal myeloproliferative condition, results from the **Philadelphia chromosome**, a specific chromosomal translocation between chromosomes 9 and 22 producing the **BCR-ABL fusion gene**, encoding a constitutively active tyrosine kinase enzyme that drives genuinely uncontrolled proliferation of the myeloid cell lineage, a specific, well-characterised molecular abnormality present in the great majority of confirmed cases.

This specific, genuinely well-understood molecular abnormality directly underlies both the confirmatory diagnostic testing and the genuinely targeted treatment approach discussed further later in this Part, representing one of the clearest examples in the whole of medicine where understanding a single, specific molecular driver of disease has directly transformed both diagnosis and treatment for the affected condition.

Fill in the blank: Chronic myeloid leukaemia results from the Philadelphia chromosome, a translocation producing the BCR-ABL fusion _____.

4.2.2 clinical presentation and diagnosis of chronic myeloid leukaemia

A genuinely insidious onset, often identified incidentally

Chronic myeloid leukaemia frequently presents insidiously, with fatigue, weight loss, and abdominal discomfort from splenomegaly, or, in a genuinely meaningful proportion of patients,

is identified incidentally on routine blood testing before symptoms have genuinely developed, and the disease characteristically progresses through three phases, chronic, accelerated, and blast phase, if left untreated, with the blast phase representing genuine transformation to a picture resembling acute leukaemia.

Diagnosis combines the characteristic blood film appearance with confirmatory genetic testing for the BCR-ABL fusion gene already discussed, and this specific genetic confirmation is genuinely essential both to establish the diagnosis with confidence and to guide the targeted treatment approach discussed in the following sub-Part, given how directly the specific molecular abnormality shapes the most appropriate treatment choice for this particular condition.

Fill in the blank: Chronic myeloid leukaemia characteristically progresses through chronic, accelerated, and _____ phases if left untreated.

4.2.3 management of chronic myeloid leukaemia

A genuinely transformative targeted therapy

Tyrosine kinase inhibitors, directly targeting the abnormal BCR-ABL protein already discussed, have genuinely transformed chronic myeloid leukaemia management, converting what was once a genuinely fatal condition into one where the great majority of appropriately treated patients now achieve genuine long-term disease control, and this specific example, alongside the biological therapies already discussed in an earlier course of this programme, illustrates the genuine, transformative power of targeted molecular therapy in modern medicine.

Ongoing molecular monitoring, tracking the specific level of residual BCR-ABL transcript over time, allows confirmation of adequate treatment response and early detection of treatment failure or disease relapse, and haematopoietic stem cell transplantation, already discussed for other conditions earlier in this course, remains reserved for patients with disease genuinely refractory to tyrosine kinase inhibitor therapy given the generally superior safety profile of the targeted medication approach.

Fill in the blank: Ongoing molecular monitoring tracks the specific level of residual BCR-ABL _____ over time.

Table 4.1: The three phases of chronic myeloid leukaemia

Phase	Key feature	Treatment implication
Chronic phase	Insidious, often incidental presentation	Most patients present at this stage

Accelerated phase	Increasing disease burden and symptoms	Signals progressing, less controlled disease
Blast phase	Transformation resembling acute leukaemia	Requires acute leukaemia-directed treatment

Pilot questions 4.2

1. Describe the Philadelphia chromosome and BCR-ABL fusion gene. (Linked to SLO 4.3)
2. Describe the typical presentation of chronic myeloid leukaemia. (Linked to SLO 4.3)
3. List the three phases of chronic myeloid leukaemia. (Linked to SLO 4.3)
4. Describe tyrosine kinase inhibitor therapy. (Linked to SLO 4.3)
5. Describe the role of ongoing molecular monitoring. (Linked to SLO 4.3)

4.3 Acute Leukaemias

4.3.1 acute myeloid leukaemia

Uncontrolled proliferation of immature myeloid precursor cells

Acute myeloid leukaemia, resulting from malignant proliferation of immature myeloid precursor cells, **blasts**, that fail to mature normally, accumulates within the bone marrow and crowds out normal haematopoiesis, producing genuine pancytopenia already discussed in relation to aplastic anaemia in Series 2, though through a genuinely distinct underlying mechanism, malignant marrow infiltration rather than marrow failure itself.

Presentation reflects this pancytopenia, fatigue from anaemia, infection from neutropenia, and bleeding from thrombocytopenia, alongside, in some cases, specific extramedullary infiltration producing gum hypertrophy or skin involvement, and acute myeloid leukaemia is the most common acute leukaemia in adults, with incidence rising considerably with advancing age, a genuinely important demographic pattern this Series aims to establish clearly.

Fill in the blank: Acute myeloid leukaemia is the most common acute leukaemia in adults, with incidence rising considerably with advancing _____.

4.3.2 acute lymphoblastic leukaemia

The most common childhood leukaemia, with a genuinely different age pattern

Acute lymphoblastic leukaemia, resulting from malignant proliferation of immature lymphoid precursor cells, is the most common childhood cancer overall, producing a genuinely similar pancytopenia-driven symptom pattern to acute myeloid leukaemia already discussed, though additionally frequently presenting with lymphadenopathy and hepatosplenomegaly reflecting the lymphoid lineage this specific leukaemia involves.

Central nervous system involvement, given the genuine tendency for lymphoblastic leukaemia cells to infiltrate this specific site, requires active investigation and, where confirmed or considered a genuine risk, specific prophylactic or therapeutic treatment directed at this location, a genuinely distinctive consideration setting acute lymphoblastic leukaemia apart from the management approach for acute myeloid leukaemia discussed in the previous sub-Part.

Fill in the blank: Central nervous system involvement requires active investigation given the genuine tendency for lymphoblastic leukaemia cells to _____ this specific site.

4.3.3 investigation and diagnosis of acute leukaemia

Confirming the diagnosis and characterising the specific leukaemia subtype

Full blood count and blood film, demonstrating pancytopenia alongside circulating blast cells, provide the initial supporting evidence for acute leukaemia, and **bone marrow biopsy and aspirate**, directly examining the marrow, confirms the diagnosis, with blast cells exceeding a genuinely defined threshold percentage of marrow cellularity required to formally confirm acute, rather than a lesser degree of, leukaemic transformation.

Immunophenotyping and cytogenetic testing, characterising the specific surface markers and genetic abnormalities of the malignant cells, distinguish acute myeloid from acute lymphoblastic leukaemia with genuine confidence and further subclassify the specific leukaemia subtype, information that directly, genuinely shapes both prognosis and the most appropriate specific treatment approach for the individual patient's confirmed diagnosis.

Fill in the blank: Immunophenotyping and cytogenetic testing distinguish acute myeloid from acute lymphoblastic leukaemia and further _____ the specific subtype.

Figure 4.2: A clinician performing a bone marrow aspirate procedure.

Pilot questions 4.3

1. Describe the pathophysiology of acute myeloid leukaemia. (Linked to SLO 4.4)
2. Describe the typical presentation of acute myeloid leukaemia. (Linked to SLO 4.4)
3. Describe acute lymphoblastic leukaemia and its typical age group. (Linked to SLO 4.4)
4. Explain why central nervous system involvement requires specific consideration in acute lymphoblastic leukaemia. (Linked to SLO 4.4)
5. Describe the investigations used to diagnose acute leukaemia. (Linked to SLO 4.5)

4.4 Management of Acute Leukaemia and Chronic Lymphocytic Leukaemia

4.4.1 management principles of acute leukaemia

Intensive, staged treatment aiming for genuine cure

Induction chemotherapy, aiming to achieve genuine remission by eliminating the great majority of leukaemic cells, is followed by **consolidation therapy**, further treatment eliminating any genuinely residual disease and reducing the risk of relapse, and, for appropriately selected patients with higher-risk disease, **haematopoietic stem cell transplantation**, already discussed

for other conditions earlier in this course, offering the genuinely greatest chance of long-term cure for this specific patient group.

This structured, staged treatment approach, genuinely intensive and demanding considerable supportive care throughout, reflects the aggressive nature of acute leukaemia itself and the correspondingly aggressive treatment genuinely required to achieve durable remission, and the specific treatment intensity and duration is genuinely individualised according to the specific leukaemia subtype, genetic risk features, and the patient's overall fitness to tolerate intensive treatment.

Fill in the blank: Consolidation therapy follows induction chemotherapy, eliminating any genuinely residual disease and reducing the risk of _____.

4.4.2 complications of acute leukaemia and its treatment

Genuine risks from both the disease itself and its treatment

Tumour lysis syndrome, a genuine metabolic emergency resulting from rapid breakdown of a large number of leukaemic cells following chemotherapy initiation, releasing intracellular contents faster than the kidneys can safely clear them, produces significant electrolyte disturbance and acute kidney injury, and active, proactive prevention, including adequate hydration and specific medication reducing uric acid production, is genuinely essential before high-risk chemotherapy is administered.

Neutropenic sepsis, life-threatening infection occurring during the genuinely profound neutropenia intensive chemotherapy produces, requires immediate recognition and urgent empirical broad-spectrum antibiotic treatment, mirroring the same genuine urgency already established for other severe infections throughout this course, and this specific combination of disease-related and treatment-related complications underlines why comprehensive supportive care remains genuinely essential throughout acute leukaemia treatment.

Fill in the blank: Neutropenic sepsis requires immediate recognition and urgent empirical broad-spectrum _____ treatment.

4.4.3 chronic lymphocytic leukaemia

A genuinely different, typically far more indolent leukaemia

Chronic lymphocytic leukaemia, the most common leukaemia overall in adults in Western populations, results from clonal proliferation of genuinely mature, though functionally abnormal, lymphocytes, and, in genuine contrast to the acute leukaemias already discussed across this

Series, frequently follows a genuinely indolent course, with many patients remaining asymptomatic for years, identified incidentally on routine blood testing rather than through symptomatic presentation.

Presentation, when symptomatic, includes lymphadenopathy, fatigue, and recurrent infection reflecting the genuine, though initially subtle, immune dysfunction this condition can produce, and management follows a genuinely individualised approach, with observation, often termed watchful waiting, appropriate for asymptomatic, early-stage disease, and treatment reserved for patients with genuinely progressive or symptomatic disease, closing this Series on the theme of matching treatment intensity to genuine disease activity that has run consistently throughout this entire course.

Fill in the blank: Watchful waiting is appropriate for asymptomatic, early-stage chronic lymphocytic leukaemia rather than immediate _____.

Table 4.2: Comparing acute myeloid leukaemia and acute lymphoblastic leukaemia

Feature	Acute myeloid leukaemia	Acute lymphoblastic leukaemia
Cell lineage	Myeloid precursor cells	Lymphoid precursor cells
Typical age group	Most common in adults, incidence rising with age	Most common childhood cancer overall
Distinctive feature	Gum hypertrophy, skin involvement in some cases	Frequent CNS involvement requiring specific treatment

Pilot questions 4.4

1. Describe induction and consolidation chemotherapy. (Linked to SLO 4.6)
2. Describe tumour lysis syndrome and its prevention. (Linked to SLO 4.7)
3. Describe neutropenic sepsis and its management. (Linked to SLO 4.7)
4. Describe chronic lymphocytic leukaemia and its typical course. (Linked to SLO 4.8)
5. Explain when watchful waiting is appropriate in chronic lymphocytic leukaemia. (Linked to SLO 4.8)

Series Summary

This Series covered myeloproliferative disorders and the major leukaemias. Part 4.1 covered polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis, while Part 4.2 turned to chronic myeloid leukaemia. Part 4.3 covered acute myeloid and acute lymphoblastic leukaemia, and Part 4.4 closed with the management of acute leukaemia and chronic lymphocytic leukaemia.

You should now be able to describe and manage myeloproliferative disorders and the major leukaemias covered across all four Parts of this Series, meeting the outcomes set for this Series. Series 5 turns next to lymphomas and myelomatosis.

Glossary of Terms

1. **Acute lymphoblastic leukaemia:** malignant proliferation of immature lymphoid precursor cells.
2. **Acute myeloid leukaemia:** malignant proliferation of immature myeloid precursor cells.
3. **BCR-ABL fusion gene:** the abnormal gene product of the Philadelphia chromosome in chronic myeloid leukaemia.
4. **Blast:** an immature precursor cell characteristic of acute leukaemia.
5. **Chronic lymphocytic leukaemia:** clonal proliferation of mature lymphocytes, often indolent in course.
6. **Chronic myeloid leukaemia:** a myeloproliferative condition driven by the Philadelphia chromosome.
7. **Neutropenic sepsis:** life-threatening infection during profound neutropenia from chemotherapy.
8. **Philadelphia chromosome:** the translocation between chromosomes 9 and 22 defining chronic myeloid leukaemia.
9. **Polycythaemia vera:** a myeloproliferative disorder of excess red cell production.
10. **Primary myelofibrosis:** the most severe myeloproliferative disorder, with progressive marrow fibrosis.
11. **Tumour lysis syndrome:** a metabolic emergency from rapid leukaemic cell breakdown after chemotherapy.
12. **Tyrosine kinase inhibitor:** targeted medication blocking the abnormal BCR-ABL protein.

Concept Check Questions [Series 4]

Objective questions

- A specific acquired mutation in the _____ gene is present in the great majority of polycythaemia vera patients. (Linked to SLO 4.1)
- Chronic myeloid leukaemia characteristically progresses through chronic, accelerated, and _____ phases if left untreated. (Linked to SLO 4.3)
- Acute myeloid leukaemia is the most common acute leukaemia in adults, with incidence rising considerably with advancing _____. (Linked to SLO 4.4)
- Consolidation therapy follows induction chemotherapy, eliminating any genuinely residual disease and reducing the risk of _____. (Linked to SLO 4.6)
- Watchful waiting is appropriate for asymptomatic, early-stage chronic lymphocytic leukaemia rather than immediate _____. (Linked to SLO 4.8)

Short-answer questions

1. Describe the presentation of polycythaemia vera. (Linked to SLO 4.2)
2. Describe the Philadelphia chromosome and BCR-ABL fusion gene. (Linked to SLO 4.3)
3. Describe acute lymphoblastic leukaemia and its typical age group. (Linked to SLO 4.4)
4. Describe tumour lysis syndrome and its prevention. (Linked to SLO 4.7)
5. Describe chronic lymphocytic leukaemia and its typical course. (Linked to SLO 4.8)

Long-answer questions

6. Discuss the classification and pathophysiology of myeloproliferative disorders, including polycythaemia vera, essential thrombocythaemia, and primary myelofibrosis. (Linked to SLO 4.1, 4.2)
7. Describe the pathophysiology, genetics, presentation, diagnosis, and management of chronic myeloid leukaemia. (Linked to SLO 4.3)
8. Discuss acute myeloid leukaemia and acute lymphoblastic leukaemia, including their investigation and diagnosis. (Linked to SLO 4.4, 4.5)
9. Describe the management principles and complications of acute leukaemia. (Linked to SLO 4.6, 4.7)
10. Discuss chronic lymphocytic leukaemia. (Linked to SLO 4.8)

Answers to Concept Check Questions [Series 4]

Objective questions

11. JAK2.
12. Blast.
13. Age.
14. Relapse.
15. Treatment.

Short-answer questions

16. Polycythaemia vera presents with headache, pruritus, facial plethora, and elevated thrombotic risk.
17. The Philadelphia chromosome is a translocation producing the BCR-ABL fusion gene, an active tyrosine kinase.
18. Acute lymphoblastic leukaemia is malignant lymphoid precursor proliferation, the most common childhood cancer.
19. Tumour lysis syndrome is rapid leukaemic cell breakdown causing electrolyte disturbance, prevented with hydration and uric acid-lowering medication.
20. Chronic lymphocytic leukaemia is mature lymphocyte proliferation, frequently following an indolent course.

Long-answer questions

21. **Basic response:** Myeloproliferative disorders result from clonal stem cell proliferation, classified by predominant lineage; polycythaemia vera causes excess red cells with thrombotic risk; essential thrombocythaemia causes excess platelets; primary myelofibrosis causes marrow fibrosis and cytopenias.

    Value-added response: A value-added response notes that the JAK2 mutation is shared across the majority of these conditions, underlying diagnostic testing.

22. **Basic response:** Chronic myeloid leukaemia results from the Philadelphia chromosome producing BCR-ABL, presenting insidiously and progressing through three phases; diagnosis uses genetic testing; management uses tyrosine kinase inhibitors.

    Value-added response: A value-added response notes that this represents one of the clearest examples of targeted molecular therapy transforming outcomes.

23. **Basic response:** Acute myeloid leukaemia involves myeloid blast proliferation, most common in adults; acute lymphoblastic leukaemia involves lymphoid blasts, most

common in children with frequent CNS involvement; diagnosis uses blood film, marrow biopsy, and immunophenotyping.

Value-added response: A value-added response notes that cytogenetic testing further subclassifies leukaemia, directly shaping prognosis and treatment.

24. **Basic response:** Management uses induction, consolidation, and, for selected patients, transplantation; complications include tumour lysis syndrome and neutropenic sepsis, requiring proactive prevention and urgent treatment respectively.

    Value-added response: A value-added response notes that treatment intensity is individualised according to leukaemia subtype and patient fitness.

25. **Basic response:** Chronic lymphocytic leukaemia is the most common adult leukaemia in Western populations, often indolent, managed with watchful waiting for asymptomatic disease and treatment reserved for progressive cases.

    Value-added response: A value-added response notes that many patients remain asymptomatic for years, identified incidentally on routine testing.

Answers to Pilot Questions [Series 4]

Part 4.1

1. Disorders are classified as polycythaemia vera, essential thrombocythaemia, or primary myelofibrosis by predominant lineage.
2. JAK2 mutation affects a key signalling protein, present in most polycythaemia vera cases and many other myeloproliferative disorders.
3. Polycythaemia vera presents with headache, pruritus, facial plethora, and elevated thrombotic risk.
4. Venesection removes blood to reduce red cell mass, directly reducing thrombotic risk.
5. Primary myelofibrosis causes marrow fibrosis with blood production occurring outside the marrow, often in the spleen.

Part 4.2

6. The Philadelphia chromosome is a translocation producing BCR-ABL, an active tyrosine kinase driving proliferation.

7. Chronic myeloid leukaemia often presents insidiously with fatigue, weight loss, and splenomegaly, or is found incidentally.
8. The three phases are chronic, accelerated, and blast phase.
9. Tyrosine kinase inhibitors directly target the abnormal BCR-ABL protein, achieving long-term disease control.
10. Molecular monitoring tracks residual BCR-ABL transcript to confirm response and detect relapse early.

Part 4.3

11. Acute myeloid leukaemia results from malignant myeloid blast proliferation crowding out normal haematopoiesis.
12. Presentation reflects pancytopenia, with fatigue, infection, and bleeding.
13. Acute lymphoblastic leukaemia is the most common childhood cancer, from malignant lymphoid blast proliferation.
14. Lymphoblastic cells have a genuine tendency to infiltrate the central nervous system, requiring specific treatment.
15. Diagnosis uses full blood count, blood film, bone marrow biopsy, and immunophenotyping.

Part 4.4

1. Induction aims to achieve remission; consolidation eliminates residual disease to reduce relapse risk.
2. Tumour lysis syndrome is rapid cell breakdown causing electrolyte disturbance, prevented with hydration and medication.
3. Neutropenic sepsis is life-threatening infection during profound neutropenia, requiring urgent empirical antibiotics.
4. Chronic lymphocytic leukaemia is mature lymphocyte proliferation, frequently indolent, sometimes asymptomatic for years.
5. Watchful waiting is appropriate for asymptomatic, early-stage disease without progression.

References and Attributions [Series 4]

1. Hoffbrand, A. V., & Steensma, D. P. (2019). Hoffbrand's Essential Haematology (8th ed.). Wiley-Blackwell.
2. Kumar, P., & Clark, M. (2020). Kumar and Clark's Clinical Medicine (10th ed.). Elsevier.
3. British Society for Haematology (2019). Guideline for the Diagnosis and Management of Chronic Myeloid Leukaemia. British Journal of Haematology.
4. British Society for Haematology (2016). Guideline for the Management of Acute Myeloid Leukaemia. British Journal of Haematology.

Figures, Plates, Tables, and Boxes

1. Figure 4.1: Facial plethora, ruddy complexion, characteristic of polycythaemia vera. AI-generated using the prompt: "Create a realistic clinical illustration titled Facial Plethora in Polycythaemia Vera, showing a patient's face with a visibly ruddy, reddened complexion, clinical examination setting, respectful and clinical in tone. Clean clinical illustration style, no text."
2. Table 4.1: The three phases of chronic myeloid leukaemia. AI-generated using the prompt: "Create a clean reference table titled The Three Phases of Chronic Myeloid Leukaemia, listing phase, key feature, and treatment implication. Simple clinical reference table style with outside border."
3. Figure 4.2: A clinician performing a bone marrow aspirate procedure. AI-generated using the prompt: "Create a realistic clinical illustration titled Bone Marrow Aspirate Procedure, showing a clinician performing a bone marrow aspiration from a patient's posterior iliac crest, patient positioned on their side, sterile drapes visible, procedure room setting. Clean clinical illustration style, no text."
4. Table 4.2: Comparing acute myeloid leukaemia and acute lymphoblastic leukaemia. AI-generated using the prompt: "Create a clean reference table titled Comparing Acute Myeloid Leukaemia and Acute Lymphoblastic Leukaemia, listing feature, acute myeloid leukaemia, and acute lymphoblastic leukaemia. Simple clinical reference table style with outside border."

Course code: MED 612

Course title: Haematology II

Course credit load: 2 Units

Series 5: Lymphomas and Myelomatosis

- **Part 5.1: Hodgkin Lymphoma**
    - Sub Part 5.1.1: Pathophysiology and pathology of Hodgkin lymphoma
    - Sub Part 5.1.2: Clinical presentation of Hodgkin lymphoma
    - Sub Part 5.1.3: Staging and management of Hodgkin lymphoma
- **Part 5.2: Non-Hodgkin Lymphoma**
    - Sub Part 5.2.1: Classification and pathophysiology of non-Hodgkin lymphoma
    - Sub Part 5.2.2: Clinical presentation of non-Hodgkin lymphoma
    - Sub Part 5.2.3: Management of non-Hodgkin lymphoma
- **Part 5.3: Myelomatosis I: Pathophysiology and Presentation**
    - Sub Part 5.3.1: Pathophysiology of myelomatosis
    - Sub Part 5.3.2: Clinical presentation of myelomatosis
    - Sub Part 5.3.3: Complications of myelomatosis
- **Part 5.4: Myelomatosis II: Diagnosis and Management**
    - Sub Part 5.4.1: Investigation and diagnosis of myelomatosis
    - Sub Part 5.4.2: Management of myelomatosis
    - Sub Part 5.4.3: Monitoring and prognosis of myelomatosis

Introduction

This final Series closes the course with the malignant lymphoid conditions, **Hodgkin lymphoma**, a genuinely distinctive lymphoid malignancy with a genuinely favourable modern prognosis, **non-Hodgkin lymphoma**, a genuinely wide, heterogeneous family of related

conditions, and **myelomatosis**, malignant plasma cell proliferation producing a genuinely distinctive, multi-system clinical picture rooted in the specific biology of the affected cell.

The aim of this Series is to equip you with an understanding of the pathophysiology, pathology, presentation, staging, and management of Hodgkin lymphoma, the classification, pathophysiology, presentation, and management of non-Hodgkin lymphoma, and the pathophysiology, presentation, complications, investigation, diagnosis, management, monitoring, and prognosis of myelomatosis.

This Series opens with **Hodgkin lymphoma**, moves through **non-Hodgkin lymphoma** and **myelomatosis I: pathophysiology and presentation**, and closes with **myelomatosis II: diagnosis and management**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 5.1:** describe the pathophysiology, pathology, and clinical presentation of Hodgkin lymphoma
- **SLO 5.2:** discuss the staging and management of Hodgkin lymphoma
- **SLO 5.3:** describe the classification, pathophysiology, and clinical presentation of non-Hodgkin lymphoma
- **SLO 5.4:** discuss the management of non-Hodgkin lymphoma
- **SLO 5.5:** describe the pathophysiology and clinical presentation of myelomatosis
- **SLO 5.6:** describe the complications of myelomatosis
- **SLO 5.7:** discuss the investigation, diagnosis, and management of myelomatosis
- **SLO 5.8:** discuss the monitoring and prognosis of myelomatosis

5.1 Hodgkin Lymphoma

5.1.1 pathophysiology and pathology of hodgkin lymphoma

A genuinely distinctive malignant cell defining the diagnosis

Hodgkin lymphoma, a malignancy of lymphoid tissue, is genuinely pathologically defined by the presence of **Reed-Sternberg cells**, large, distinctive malignant cells with a characteristic binucleate or multinucleate appearance, within an otherwise predominantly reactive, non-malignant inflammatory cell background, a genuinely unique histological pattern distinguishing

Hodgkin lymphoma from the non-Hodgkin lymphomas discussed in the following Part of this Series.

Hodgkin lymphoma shows a genuinely characteristic bimodal age distribution, with peaks in young adulthood and again in older age, and, though its precise underlying trigger remains genuinely incompletely understood, a recognised association with prior Epstein-Barr virus infection exists in a meaningful proportion of cases, contributing to the current understanding of this condition's underlying pathophysiology.

Fill in the blank: Hodgkin lymphoma is genuinely pathologically defined by the presence of _____ cells.

5.1.2 clinical presentation of hodgkin lymphoma

Painless lymphadenopathy, and genuinely characteristic systemic symptoms

Painless lymphadenopathy, most commonly cervical, is the classic presenting feature of Hodgkin lymphoma, and **B symptoms**, fever, drenching night sweats, and unintentional weight loss, occur in a genuinely meaningful proportion of patients, carrying direct prognostic significance and forming part of the formal staging classification discussed in the following sub-Part of this Part.

Alcohol-induced lymph node pain, a genuinely distinctive though relatively uncommon feature where affected lymph nodes become painful shortly after alcohol consumption, is a specific finding worth recognising given its genuine, though not perfectly sensitive, diagnostic value, and pruritus, generalised itching without an obvious dermatological cause, further completes the genuinely characteristic clinical picture this Part aims to establish.

Fill in the blank: B symptoms include fever, drenching night sweats, and unintentional _____ loss.

5.1.3 staging and management of hodgkin lymphoma

A genuinely, meaningfully curable malignancy in the great majority of cases

Staging, using the Ann Arbor system, assessing the number and location of involved lymph node regions and the presence or absence of extranodal or B symptom involvement already discussed, combined with cross-sectional and functional imaging, directly determines the specific treatment approach, and this structured staging framework directly parallels the staging principles already established for other malignancies discussed elsewhere in this programme.

Combination chemotherapy, with or without radiotherapy depending on the specific stage and disease characteristics, achieves genuine cure in the great majority of patients with Hodgkin lymphoma, representing one of the genuinely most successful examples in the whole of oncology of a malignancy transformed from a historically fatal diagnosis to one with a genuinely excellent overall prognosis through modern, evidence-based treatment.

Fill in the blank: Combination chemotherapy achieves genuine cure in the great majority of patients with Hodgkin _____.

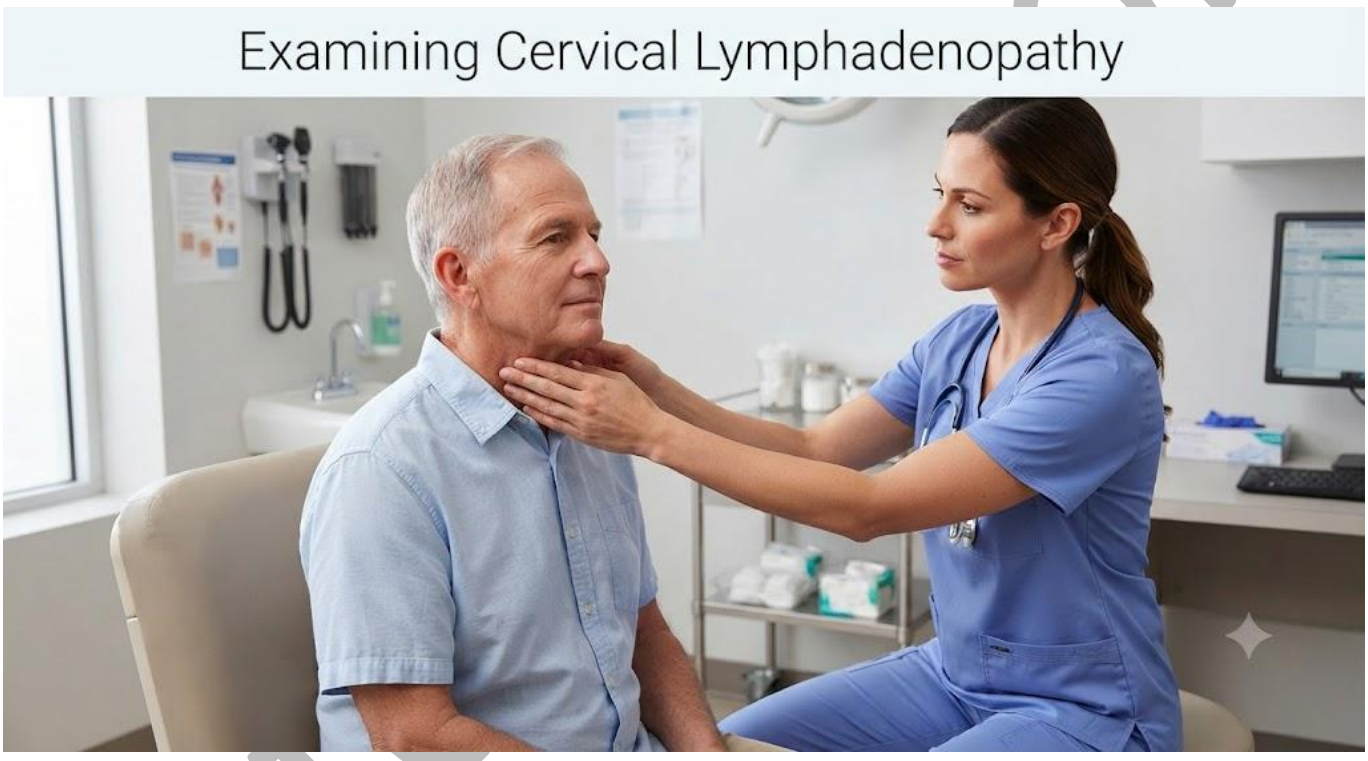

Figure 5.1: A clinician examining a patient's neck for cervical lymphadenopathy.

Pilot questions 5.1

- Describe Reed-Sternberg cells and their diagnostic significance. (Linked to SLO 5.1)
- Describe the age distribution of Hodgkin lymphoma. (Linked to SLO 5.1)
- Describe B symptoms and their significance. (Linked to SLO 5.1)
- Describe the Ann Arbor staging system. (Linked to SLO 5.2)
- Describe the general management approach and prognosis of Hodgkin lymphoma. (Linked to SLO 5.2)

5.2 Non-Hodgkin Lymphoma

5.2.1 classification and pathophysiology of non-hodgkin lymphoma

A genuinely wide, heterogeneous family of related malignancies

Non-Hodgkin lymphoma, encompassing a genuinely wide, heterogeneous group of lymphoid malignancies lacking the Reed-Sternberg cells already discussed for Hodgkin lymphoma, is broadly classified by cell of origin, B-cell or T-cell, and by clinical behaviour, **indolent**, slow-growing, or **aggressive**, rapidly progressive, a genuinely important distinction directly shaping both the urgency of treatment and the overall prognosis for a given specific subtype.

Diffuse large B-cell lymphoma, the most common aggressive subtype, and **follicular lymphoma**, a genuinely common indolent subtype, together illustrate the genuine spectrum this diverse condition spans, and specific chromosomal translocations and other molecular abnormalities, genuinely distinct from the Philadelphia chromosome already discussed for chronic myeloid leukaemia in an earlier Series, underlie many specific non-Hodgkin lymphoma subtypes.

Fill in the blank: Non-Hodgkin lymphoma is classified by clinical behaviour as indolent, slow-growing, or _____, rapidly progressive.

5.2.2 clinical presentation of non-hodgkin lymphoma

A genuinely wide-ranging presentation reflecting the heterogeneous disease group

Presentation genuinely varies considerably across the wide spectrum of non-Hodgkin lymphoma subtypes already discussed, though lymphadenopathy, sometimes painless similar to Hodgkin lymphoma but often multiple, non-contiguous nodal regions rather than the more typically contiguous spread pattern of Hodgkin lymphoma, remains a genuinely common presenting feature, alongside B symptoms already discussed in the previous Part, occurring in a meaningful proportion of affected patients.

Extranodal involvement, disease occurring outside the lymph nodes themselves, including the gastrointestinal tract, skin, and central nervous system, occurs considerably more commonly in non-Hodgkin lymphoma than in Hodgkin lymphoma, reflecting the genuinely wider anatomical distribution non-Hodgkin lymphoma subtypes can adopt, and this specific feature carries genuine diagnostic and prognostic significance depending on the specific site involved.

Fill in the blank: Extranodal involvement occurs considerably more commonly in non-Hodgkin lymphoma than in _____ lymphoma.

5.2.3 management of non-hodgkin lymphoma

A genuinely individualised approach reflecting the diverse disease spectrum

Management is genuinely individualised according to the specific subtype, its indolent or aggressive behaviour already discussed, and the patient's overall fitness, with aggressive subtypes typically requiring prompt combination chemotherapy, often combined with a specific monoclonal antibody targeting a surface marker present on many B-cell lymphomas, while indolent subtypes may be genuinely appropriate for observation, watchful waiting already introduced for chronic lymphocytic leukaemia in an earlier Series, in appropriately selected, asymptomatic patients.

Monoclonal antibody therapy, targeting specific surface proteins expressed on malignant lymphoid cells, has genuinely transformed non-Hodgkin lymphoma treatment in recent decades, mirroring the same transformative impact of targeted molecular therapy already discussed for chronic myeloid leukaemia earlier in this course, and this combined chemoimmunotherapy approach now forms the genuine backbone of treatment for the great majority of B-cell non-Hodgkin lymphoma subtypes.

Fill in the blank: Monoclonal antibody therapy targets specific surface proteins expressed on malignant lymphoid _____.

Table 5.1: Comparing Hodgkin and non-Hodgkin lymphoma

Feature	Hodgkin lymphoma	Non-Hodgkin lymphoma
Defining cell	Reed-Sternberg cell present	Reed-Sternberg cell absent
Nodal spread pattern	Typically contiguous	Often non-contiguous
Extranodal involvement	Less common	Considerably more common

Pilot questions 5.2

1. Describe the classification of non-Hodgkin lymphoma. (Linked to SLO 5.3)
2. Distinguish indolent from aggressive non-Hodgkin lymphoma. (Linked to SLO 5.3)
3. Describe the typical presentation of non-Hodgkin lymphoma. (Linked to SLO 5.3)
4. Describe extranodal involvement and its significance. (Linked to SLO 5.3)
5. Describe monoclonal antibody therapy in non-Hodgkin lymphoma management. (Linked to SLO 5.4)

5.3 Myelomatosis I: Pathophysiology and Presentation

5.3.1 pathophysiology of myelomatosis

Malignant plasma cells producing a genuinely abnormal, monoclonal protein

Myelomatosis, also termed multiple myeloma, results from malignant proliferation of a single clone of plasma cells within the bone marrow, producing excess **monoclonal immunoglobulin**, termed **paraprotein**, a genuinely characteristic, single specific antibody type rather than the normal, diverse antibody repertoire healthy plasma cells collectively produce, directly underlying the specific diagnostic testing discussed later in this Series.

This malignant plasma cell proliferation produces genuinely wide-ranging effects, directly infiltrating and disrupting normal bone marrow function, producing localised bone destruction through activation of osteoclasts, cells responsible for normal bone resorption, and, through the excess paraprotein itself, contributing to several of the genuinely characteristic complications discussed in the closing sub-Part of this Part.

Fill in the blank: Myelomatosis produces excess monoclonal immunoglobulin, termed _____.

5.3.2 clinical presentation of myelomatosis

A genuinely wide-ranging presentation reflecting multiple underlying mechanisms

Bone pain, particularly affecting the back and ribs, reflecting the osteoclast-mediated bone destruction already discussed, is a genuinely common presenting symptom, alongside fatigue from anaemia given the malignant marrow infiltration disrupting normal haematopoiesis, already discussed in principle for the leukaemias covered in the previous Series of this course, though through a genuinely distinct underlying malignant cell type.

Recurrent infection, reflecting genuinely impaired normal antibody production despite the excess paraprotein itself, since the malignant clone crowds out the normal, diverse plasma cell population responsible for a genuinely effective, broad immune response, further characterises myelomatosis presentation, and this genuinely counterintuitive combination, excess antibody production alongside functional immune deficiency, is a genuinely distinctive feature this condition demonstrates.

Fill in the blank: Recurrent infection in myelomatosis reflects genuinely impaired normal antibody production despite excess _____.

5.3.3 complications of myelomatosis

A genuinely characteristic combination, commonly remembered together

The genuinely characteristic complications of myelomatosis, sometimes remembered together as a specific combination, include **hypercalcaemia** from the osteoclast-mediated bone destruction already discussed, **renal impairment**, resulting from several mechanisms including direct paraprotein-related kidney damage and the hypercalcaemia itself, **anaemia** from marrow infiltration already discussed, and **bone lesions**, the characteristic lytic, punched-out bone destruction visible on imaging.

Recognising this genuinely characteristic combination of complications should immediately raise clinical suspicion for underlying myelomatosis in an older patient, since myelomatosis predominantly affects older adults, presenting with any combination of unexplained bone pain, renal impairment, anaemia, or hypercalcaemia, rather than pursuing each specific complication as an entirely separate, unrelated clinical problem.

Fill in the blank: Myelomatosis produces characteristic lytic, punched-out bone destruction visible on _____.

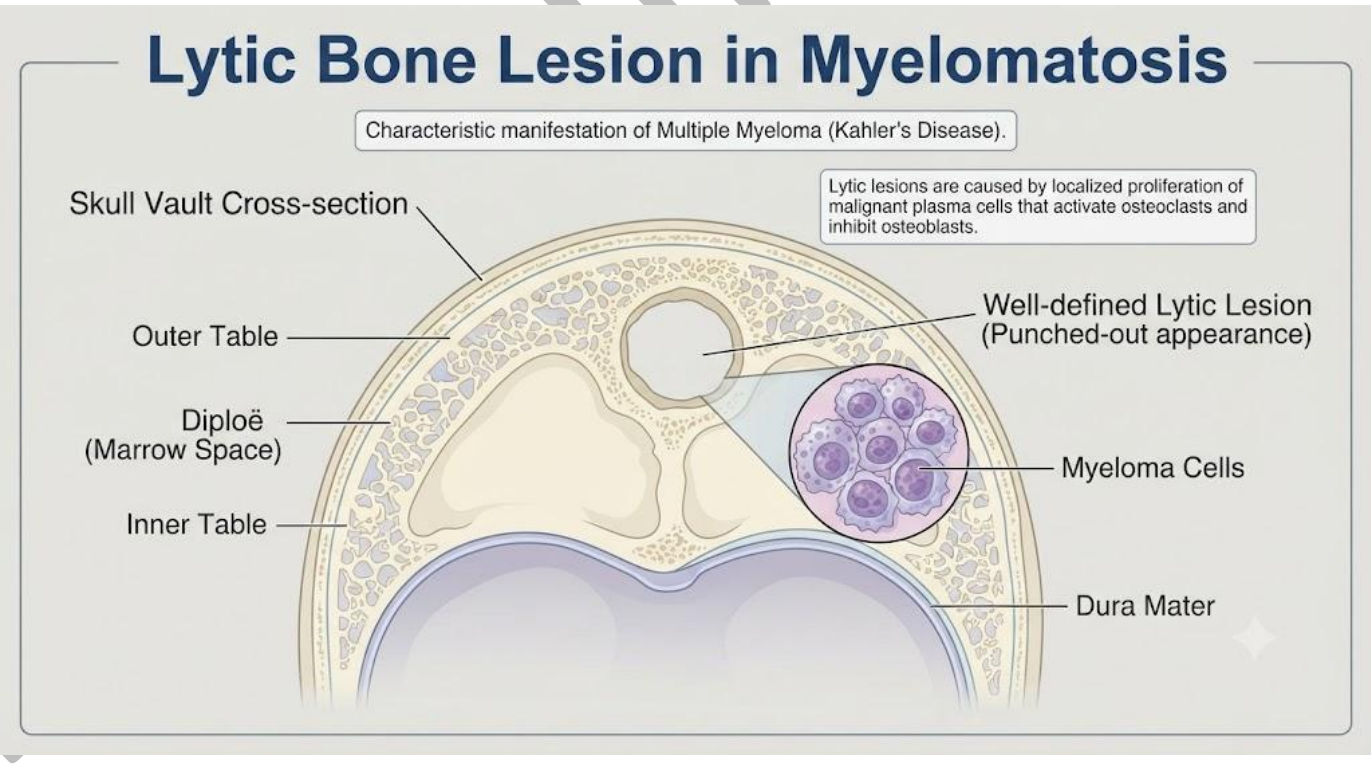

Figure 5.2: A labelled diagram of a lytic, punched-out bone lesion characteristic of myelomatosis.

Pilot questions 5.3

1. Describe the pathophysiology of myelomatosis. (Linked to SLO 5.5)
2. Describe paraprotein. (Linked to SLO 5.5)
3. Describe the typical presentation of myelomatosis. (Linked to SLO 5.5)
4. Explain why myelomatosis causes recurrent infection despite excess antibody production. (Linked to SLO 5.5)
5. List the characteristic complications of myelomatosis. (Linked to SLO 5.6)

5.4 Myelomatosis II: Diagnosis and Management

5.4.1 investigation and diagnosis of myelomatosis

Confirming the paraprotein and the underlying marrow infiltration

Serum and urine protein electrophoresis, identifying the characteristic monoclonal paraprotein already discussed, alongside **serum free light chain assay**, measuring a specific component of the paraprotein with genuine additional diagnostic and monitoring value, and **bone marrow biopsy**, confirming genuine clonal plasma cell infiltration, together form the essential diagnostic panel for confirming myelomatosis.

Skeletal imaging, using whole-body low-dose computed tomography or magnetic resonance imaging in preference to older plain radiographic skeletal survey techniques given their genuinely superior sensitivity, identifies the characteristic lytic bone lesions already discussed, and formal diagnostic criteria combine the specific laboratory and imaging findings already discussed with evidence of genuine end-organ damage before a confident diagnosis of active, treatment-requiring myelomatosis is confirmed.

Fill in the blank: Serum free light chain assay measures a specific component of the paraprotein with genuine additional diagnostic and _____ value.

5.4.2 management of myelomatosis

A genuinely individualised, multi-agent treatment approach

Combination chemotherapy, typically incorporating a proteasome inhibitor, an immunomodulatory agent, and corticosteroids, forms the current standard initial treatment approach for myelomatosis, and, for appropriately selected, typically younger, fitter patients,

autologous stem cell transplantation, using the patient's own previously collected stem cells following high-dose chemotherapy, offers genuinely improved depth and durability of disease response compared with chemotherapy alone.

Supportive management of the specific complications already discussed earlier in this Series, bisphosphonate therapy reducing further bone destruction and fracture risk, management of hypercalcaemia and renal impairment following the same general principles already established elsewhere in this course, and prompt treatment of infection given the genuine immune dysfunction already discussed, forms a genuinely essential, comprehensive component of care alongside the disease-directed treatment itself.

Fill in the blank: Autologous stem cell transplantation uses the patient's own previously collected stem cells following high-dose _____.

5.4.3 monitoring and prognosis of myelomatosis

A genuinely chronic, relapsing-remitting disease course

Myelomatosis genuinely, characteristically follows a relapsing-remitting course, with periods of disease control interspersed with genuine relapse requiring further treatment, and ongoing monitoring, tracking the specific paraprotein level and other disease markers already discussed earlier in this Series over time, allows early identification of relapse before significant, symptomatic disease progression genuinely develops.

While myelomatosis genuinely remains an incurable condition for the great majority of affected patients despite modern treatment advances, overall prognosis has meaningfully improved considerably in recent decades through the combination of proteasome inhibitors, immunomodulatory agents, and stem cell transplantation already discussed, closing this Series, and the entire course, on the same theme of continually evolving, evidence-based treatment that has run consistently throughout this whole programme of haematological study.

Fill in the blank: Myelomatosis genuinely, characteristically follows a relapsing-remitting course requiring ongoing _____.

Table 5.2: Complications and management focus in myelomatosis

Complication	Underlying mechanism	Key management focus
Hypercalcaemia	Osteoclast-mediated bone destruction	Hydration, bisphosphonate therapy
Renal impairment	Paraprotein-related damage, hypercalcaemia	Address underlying cause, supportive care

Anaemia	Marrow infiltration by malignant plasma cells	Address underlying disease, supportive care

Pilot questions 5.4

1. Describe the diagnostic panel used to confirm myelomatosis. (Linked to SLO 5.7)
2. Describe skeletal imaging in myelomatosis and its preferred modality. (Linked to SLO 5.7)
3. Describe combination chemotherapy for myelomatosis. (Linked to SLO 5.7)
4. Describe autologous stem cell transplantation. (Linked to SLO 5.7)
5. Describe the typical disease course and prognosis of myelomatosis. (Linked to SLO 5.8)

Series Summary

This final Series closed the course with the malignant lymphoid conditions. Part 5.1 covered the pathophysiology, presentation, staging, and management of Hodgkin lymphoma, while Part 5.2 turned to non-Hodgkin lymphoma. Part 5.3 covered the pathophysiology, presentation, and complications of myelomatosis, and Part 5.4 closed with its investigation, diagnosis, management, monitoring, and prognosis.

You should now be able to describe and manage Hodgkin lymphoma, non-Hodgkin lymphoma, and myelomatosis across all four Parts of this Series, meeting the outcomes set for this Series. Across the full course, Series 1 covered nutritional and haemolytic anaemias, Series 2 covered aplastic anaemia and haemoglobinopathies, Series 3 covered bleeding disorders and haematological manifestations of chronic disease, Series 4 covered myeloproliferative disorders and leukaemias, and this Series has closed the course with lymphomas and myelomatosis, together forming a comprehensive foundation in Haematology II.

Glossary of Terms

1. **Ann Arbor staging system:** a framework staging Hodgkin lymphoma by nodal involvement and symptoms.
2. **Autologous stem cell transplantation:** transplantation using a patient's own previously collected stem cells.

3. **B symptoms:** fever, night sweats, and weight loss, carrying prognostic significance in lymphoma.
4. **Diffuse large B-cell lymphoma:** the most common aggressive non-Hodgkin lymphoma subtype.
5. **Extranodal involvement:** lymphoma occurring outside the lymph nodes, more common in non-Hodgkin lymphoma.
6. **Hodgkin lymphoma:** a lymphoid malignancy defined by the presence of Reed-Sternberg cells.
7. **Myelomatosis:** malignant plasma cell proliferation producing excess monoclonal paraprotein.
8. **Non-Hodgkin lymphoma:** a heterogeneous group of lymphoid malignancies lacking Reed-Sternberg cells.
9. **Paraprotein:** the characteristic monoclonal immunoglobulin produced in myelomatosis.
10. **Proteasome inhibitor:** a class of medication forming part of standard myelomatosis treatment.
11. **Reed-Sternberg cell:** the large, distinctive malignant cell defining Hodgkin lymphoma.
12. **Serum free light chain assay:** a test measuring a specific paraprotein component in myelomatosis.

Concept Check Questions [Series 5]

Objective questions

- Hodgkin lymphoma is genuinely pathologically defined by the presence of _____ cells. (Linked to SLO 5.1)
- Non-Hodgkin lymphoma is classified by clinical behaviour as indolent, slow-growing, or _____, rapidly progressive. (Linked to SLO 5.3)
- Myelomatosis produces excess monoclonal immunoglobulin, termed _____. (Linked to SLO 5.5)
- Myelomatosis produces characteristic lytic, punched-out bone destruction visible on _____. (Linked to SLO 5.6)
- Myelomatosis genuinely, characteristically follows a relapsing-remitting course requiring ongoing _____. (Linked to SLO 5.8)

Short-answer questions

1. Describe B symptoms and their significance. (Linked to SLO 5.1)
2. Distinguish indolent from aggressive non-Hodgkin lymphoma. (Linked to SLO 5.3)

3. Explain why myelomatosis causes recurrent infection despite excess antibody production. (Linked to SLO 5.5)
4. List the characteristic complications of myelomatosis. (Linked to SLO 5.6)
5. Describe autologous stem cell transplantation. (Linked to SLO 5.7)

Long-answer questions

6. Discuss the pathophysiology, pathology, presentation, staging, and management of Hodgkin lymphoma. (Linked to SLO 5.1, 5.2)
7. Describe the classification, pathophysiology, presentation, and management of non-Hodgkin lymphoma. (Linked to SLO 5.3, 5.4)
8. Discuss the pathophysiology, presentation, and complications of myelomatosis. (Linked to SLO 5.5, 5.6)
9. Describe the investigation, diagnosis, and management of myelomatosis. (Linked to SLO 5.7)
10. Discuss the monitoring and prognosis of myelomatosis. (Linked to SLO 5.8)

Answers to Concept Check Questions [Series 5]

Objective questions

11. Reed-Sternberg.
12. Aggressive.
13. Paraprotein.
14. Imaging.
15. Monitoring.

Short-answer questions

16. B symptoms are fever, night sweats, and weight loss, carrying prognostic significance and forming part of staging.
17. Indolent lymphoma is slow-growing, while aggressive lymphoma is rapidly progressive.
18. The malignant clone crowds out normal, diverse plasma cells needed for a genuinely effective broad immune response.
19. Complications include hypercalcaemia, renal impairment, anaemia, and bone lesions.
20. Autologous transplantation uses the patient's own previously collected stem cells after high-dose chemotherapy.

Long-answer questions

21. **Basic response:** Hodgkin lymphoma is defined by Reed-Sternberg cells, presenting with painless lymphadenopathy and B symptoms; staging uses the Ann Arbor system; management with combination chemotherapy achieves cure in the great majority of patients.

    Value-added response: A value-added response notes the genuinely characteristic bimodal age distribution and Epstein-Barr virus association.

22. **Basic response:** Non-Hodgkin lymphoma is classified by cell origin and indolent or aggressive behaviour, presenting with lymphadenopathy and frequent extranodal involvement; management combines chemotherapy with monoclonal antibody therapy, individualised by subtype.

    Value-added response: A value-added response notes that indolent subtypes may be appropriate for watchful waiting in selected asymptomatic patients.

23. **Basic response:** Myelomatosis is malignant plasma cell proliferation producing paraprotein, presenting with bone pain, anaemia, and recurrent infection; complications include hypercalcaemia, renal impairment, anaemia, and bone lesions.

    Value-added response: A value-added response notes the genuinely counterintuitive combination of excess antibody production alongside functional immune deficiency.

24. **Basic response:** Diagnosis combines protein electrophoresis, free light chain assay, bone marrow biopsy, and skeletal imaging; management uses combination chemotherapy and, for selected patients, autologous stem cell transplantation.

    Value-added response: A value-added response notes that supportive management of complications forms an essential complement to disease-directed treatment.

25. **Basic response:** Myelomatosis follows a relapsing-remitting course requiring ongoing monitoring of paraprotein levels; prognosis remains incurable for most but has meaningfully improved with modern treatment.

    Value-added response: A value-added response notes that proteasome inhibitors, immunomodulatory agents, and transplantation together have transformed outcomes in recent decades.

Answers to Pilot Questions [Series 5]

Part 5.1

1. Reed-Sternberg cells are large, distinctive malignant cells that pathologically define the diagnosis.
2. Hodgkin lymphoma shows a bimodal age distribution, peaking in young adulthood and again in older age.
3. B symptoms are fever, night sweats, and weight loss, carrying prognostic significance.
4. The Ann Arbor system stages disease by nodal region involvement and presence of extranodal or B symptom involvement.
5. Combination chemotherapy with or without radiotherapy achieves genuine cure in the great majority of patients.

Part 5.2

6. Non-Hodgkin lymphoma is classified by cell of origin, B-cell or T-cell, and by clinical behaviour.
7. Indolent lymphoma is slow-growing, while aggressive lymphoma is rapidly progressive.
8. Presentation includes lymphadenopathy, often non-contiguous, alongside B symptoms in a meaningful proportion of patients.
9. Extranodal involvement occurs considerably more commonly than in Hodgkin lymphoma, carrying diagnostic and prognostic significance.
10. Monoclonal antibody therapy targets specific surface proteins on malignant cells, transforming treatment outcomes.

Part 5.3

11. Myelomatosis results from malignant plasma cell proliferation producing excess monoclonal immunoglobulin.
12. Paraprotein is a single, specific monoclonal antibody type produced by the malignant plasma cell clone.
13. Presentation includes bone pain, fatigue from anaemia, and recurrent infection.
14. The malignant clone crowds out normal, diverse plasma cells needed for effective broad immunity.
15. Complications include hypercalcaemia, renal impairment, anaemia, and bone lesions.

Part 5.4

1. The panel includes protein electrophoresis, free light chain assay, and bone marrow biopsy.

2. Skeletal imaging uses whole-body low-dose CT or MRI, preferred over older plain radiographic survey.
3. Combination chemotherapy typically incorporates a proteasome inhibitor, immunomodulatory agent, and corticosteroids.
4. Autologous transplantation uses the patient's own previously collected stem cells after high-dose chemotherapy.
5. The disease follows a relapsing-remitting course, remaining incurable for most despite meaningfully improved modern prognosis.

References and Attributions [Series 5]

1. Hoffbrand, A. V., & Steensma, D. P. (2019). Hoffbrand's Essential Haematology (8th ed.). Wiley-Blackwell.
2. Kumar, P., & Clark, M. (2020). Kumar and Clark's Clinical Medicine (10th ed.). Elsevier.
3. British Society for Haematology (2019). Guideline for the Diagnosis and Management of Hodgkin Lymphoma. British Journal of Haematology.
4. International Myeloma Working Group (2014). Criteria for the Diagnosis of Multiple Myeloma. The Lancet Oncology.

Figures, Plates, Tables, and Boxes

1. Figure 5.1: A clinician examining a patient's neck for cervical lymphadenopathy. AI-generated using the prompt: "Create a realistic clinical illustration titled Examining Cervical Lymphadenopathy, showing a clinician gently palpating the sides of a seated patient's neck, clinical examination room setting. Clean clinical illustration style, no text."
2. Table 5.1: Comparing Hodgkin and non-Hodgkin lymphoma. AI-generated using the prompt: "Create a clean reference table titled Comparing Hodgkin and Non-Hodgkin Lymphoma, listing feature, Hodgkin lymphoma, and non-Hodgkin lymphoma. Simple clinical reference table style with outside border."
3. Figure 5.2: A labelled diagram of a lytic, punched-out bone lesion characteristic of myelomatosis. AI-generated using the prompt: "Create a clean, accurate labelled educational diagram titled Lytic Bone Lesion in Myelomatosis, showing a cross-section

of skull bone with a labelled, well-defined punched-out area of bone destruction. Educational anatomical diagram style, no photographic content."

4. Table 5.2: Complications and management focus in myelomatosis. AI-generated using the prompt: "Create a clean reference table titled Complications and Management Focus in Myelomatosis, listing complication, underlying mechanism, and key management focus. Simple clinical reference table style with outside border."